A STUDY ON SOLUBILITY AND DISSOLUTION ENHANCEMENT OF ROXITHROMYCIN

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In partial fulfillment of the requirement for the award of the degree of

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IN

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By

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EXAMINER:

1.

2.

DECLARATION

The work presented in this thesis entitled **"A STUDY ON SOLUBILITY AND DISSOLUTION ENHANCEMENT OF ROXITHROMYCIN".** Was carried out by me in the department of Pharmaceutics, Arulmigu Kalasalingam College of Pharmacy, Krishnankoil. Under the direct supervision of **Mr.J.Anburaj M.Pharm.,** Department of Pharmaceutics, Arulmigu Kalasalingam College of Pharmacy, Krishnankoil.

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"**You will meet more angels on a winding path than on a straight one"**

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AFFECTIONATELY DEDICATED TO MY BELOVED PARENTS AND TO THE ALMIGHTY

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LIST OF ABBREVIATIONS USED

API	-	Active pharmaceutical ingredient
AR	-	Analytical grade
BCS	-	Bio Pharmaceutical Classification of drugs
BP	-	British Pharmacopoeia
°C	-	Degree Celsius
SSG	-	Sodium Starch Glycolate.
Conc.	-	Concentration
g	-	gram
EP	-	European Pharmacopoeia
F	-	Formulation
GIT	-	Gastro intestinal tract
HCl	-	Hydrochloric acid
LOD	-	Loss on Drying
mg	-	Milligram
MCC	-	Micro crystalline Cellulose
mL	-	Millilitre
mM	-	Millimole
mins	-	Minutes
ND	-	Not detectable
NLT	-	Not less than
NMT	-	Not more than
P^H	-	Negative logarithm of hydrogen ion

q.s.	-	Quantity sufficient
USP	-	United States Pharmacopoeia
VLDL	-	very low density lipoprotein
Wt	-	Weight
w/w	-	Weight by Weight
w/v	-	Weight by Volume

INTRODUCTION

INDRODUCTION

INTRODUCTION:

Modern pharmaceutical technology is concentrated on new drug forms which are targeted to the exact site at the appropriate time, with maximum efficiency and with reduced side-effects. Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. According to recent estimates, nearly 40% of new chemical entities are rejected because of poor solubility i.e. biopharmaceutical properties.[1]

The solubility properties of drugs and the dissolution of the active substance from dosage forms have a basic impact on the bioavailability of the product. Enhancement of the solubility of poorly-soluble drug substances is one of the most important tasks in pharmaceutical formulation development.[2] The drug substances are categorized into four classes based on their solubility parameter and permeability to bio-membranes, and such a classification system is called as a Biopharmaceutical Classification System (BCS). The BCS guidance takes into account three major factors, dissolution, solubility, and intestinal permeability, which govern the rate and extent of drug absorption from immediate release solid dosage forms. The concept of BCS provides a better understanding of the relationship between drug release from the product and the absorption process. [3]

BIOPHARMACEUTICAL CLASSIFICATION OF DRUGS (BCS):

The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability [4]. It allows for the prediction of in-vivo pharmacokinetics for oral immediate release (IR) drug products by classifying drug compounds into four classes. The in-vivo performance of orally administered drugs depends upon their solubility and tissue permeability characteristics. The release rate or solubility of the drug substance will not be a governing parameter if the absorption of the drug is permeation rate limited and in such cases the in-vitro dissolution study can be used to demonstrate the bioavailability (BA) or

bioequivalence (BE) of the drug product through in vitro - in vivo correlation (IVIVC).

Class	Solubility	Permeability
I	High	High
II	Low	High
III	High	Low
IV	Low	Low

Table No 1:BCS classification of Drugs

Class-I Drugs:

The drugs of this class exhibit high absorption number and high dissolution number. These compounds are well absorbed, and their absorption rate is usually higher than the excretion rate. In in-vivo, these drugs behave like an oral solution having fast dissolution and rapid bioavailability. Since the dissolution and absorption of class I drugs is very fast, bioavailability and bioequivalence are unnecessary for the products of such drugs. These drugs are good candidates for controlled drug delivery if they qualify pharmacokinetically and pharmacodynamically for the purpose. Gastric emptying is often the rate governing parameter in this case. Examples include Metoprolol, Diltiazem, Verapamil, Propanolol etc.. [5]

Class-II Drugs:

The drugs of this class have a high absorption number but a low dissolution number. In-vivo drug dissolution is then a rate limiting step for absorption except at a very high dose number. Drugs belonging to this class have low solubility and high permeability, hence, the dissolution rate becomes the governing parameter for bioavailability. In-vitro - in-vivo correlation (IVIVC) is usually accepted for this class of drugs. The bioavailability of these products is limited by their salvation rates. Hence, a correlation between the in-vivo bioavailability and the in-vitro salvation can be found. These drugs exhibit variable bioavailability and need enhancement in the

dissolution rate by different methods (These are also suitable for controlled release development. Examples include Gibenclamide, Phenytoin, Danazol, Mefenamic acid.

Class-III Drugs:

Permeation through the intestinal membrane forms the rate-determining step for these drugs. Since absorption is permeation rate limited, bioavailability is independent of drug release from the dosage form. For example, the various ranitidine products having different dissolution profiles produce super imposable plasma concentration versus time profile in-vivo. These drugs generally exhibit low bioavailability and permeability enhancement is generally required. These drugs are problematic for controlled release development. [5]

Class-IV Drugs:

Drugs of this class exhibit poor and variable bioavailability. The overall bioavailability is governed by several factors such as rate of dissolution, intestinal permeability, gastric emptying, and so on. These drugs are generally not suitable for oral drug delivery or else some special drug delivery technologies such as nanosuspensions will be needed. Examples include Hydrochlorothiazide, Taxol, Frusemide.amples include Cimetidine, Ranitidine, Cyclovir, Neomycin B etc.[5]

SOLUBILITY AND DISSOLUTION:

Solubility is a physicochemical property of a substance that can be generally defined as the highest amount of a substance that can be dissolved in a solvent, at a constant temperature and pressure.More specifically, solubility is considered to be the concentration that a solute reaches in a solution when equilibrium exists between the solid phase and the solution phase (saturated solution) at a defined temperature and pressure.[6]

Dissolution is the process by which a substance becomes dissolved in a solvent. Dissolution takes place when a solid substance comes in contact with molecules of a compatible solvent. [7]

Due to this major reason Solubility enhancement is one of the important parameters which should be considered in formulation development of orally administered drug with poor aqueous solubility [8]. Solubility is the characteristic

physical property referring to the ability of a given substance, the solute, to dissolve in a solvent.

Solvent – The component which forms major constituent of a solution & is capable to dissolve another substance to form a uniformly disperse mixture at the molecular level [9].

Solute – A substance that present in small quantity & dissolves in solvent [9]. "The solubility of a solute is the maximum quantity of solute that can dissolve in a certain quantity of solvent or quantity of solution at a specified temperature." In the other words, "solubility can also define as the ability of one substance to form a solution with another substance." [10]

Solubility definition in the United States of Pharmacopoeia:

Description Forms (Solubility Definition)	Parts of Solvent Required for One Part of Solute
Very soluble	<1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble	>10,000

Table No 2: Solubility definition in the united states of pharmacopoeia

Solubility and Bioavailability Enhancement:

Improve the solubility and bioavailability of poorly soluble drugs by using various approaches like physical, chemical and others modifications or techniques.

The solubility of a solute is the maximum quantity of solute that can dissolve in a certain quantity of solvent or quantity of solution at a specified temperature. [11]

Importance of Solubility

The major challenge with the design of oral dosage forms lies with their poor bioavailability. The oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, presystemic metabolism, and susceptibility to efflux mechanisms. The most frequent causes of low oral bioavailability are attributed to poor solubility and low permeability. [12].

Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for achieving required pharmacological response [13]. Poorly water soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as generic development. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. Water is the solvent of choice for liquid pharmaceutical formulations. Most of the drugs are either weakly acidic or weakly basic having poor aqueous solubility. More than 40% NCEs (new chemical entities) developed in pharmaceutical industry are practically insoluble in water. These poorly water soluble drugs having slow drug absorption leads to inadequate and variable bioavailability and gastrointestinal mucosal toxicity. For orally administered drugs solubility is the most important one rate limiting parameter to achieve their desired concentration in systemic circulation for pharmacological response. Problem of solubility is a major challenge for formulation scientist [14]. The improvement of drug solubility thereby its oral bioavailability remains one of the most challenging aspects of drug development process especially for oral-drug delivery system. There are numerous approaches available and reported in literature to enhance the solubility of poorly water-soluble drugs. The techniques are chosen on the basis of certain aspects such as properties of drug under consideration, nature of excipients to be selected, and nature of intended dosage form. The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastrointestinal fluids often cause insufficient bioavailability. Especially for class II (low solubility and high

permeability) substances according to the BCS, the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastrointestinal fluids. As for BCS class II drugs rate limiting step is drug release from the dosage form and solubility in the gastric fluid and not the absorption, so increasing the solubility in turn increases the bioavailability for BCS class II drugs [15].

PROCESS OF SOLUBLISATION:

The process of solublisation involves the breaking of inter-ionic or intermolecular bonds in the solute [16], the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion [17].

Figure no:1

Step 1: Holes opens in the solvent

Figure no:2

Step2: Molecules of the solid breaks away from the bulk

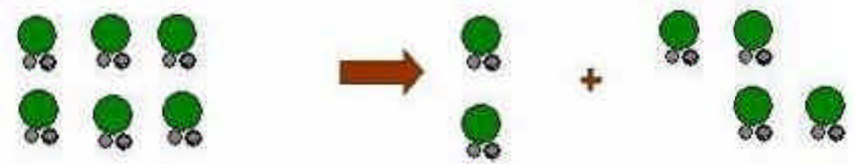


Figure no:3

Step 3: The freed solid molecule is integrated into the hole in the solvent

FACTOR AFFECTING THE SOLUBILITY

1. **Nature of solute and solvent:**

The nature of solute and solvent depends on concentration of solute in specific quantity of solvent at specific temperature. Example: at room temperature in 100gm of water only 1gm of lead (II) chloride can be dissolved while 200 grams of zinc chloride can be dissolved. [18]

2. Particle size:

Particle size affect on solubility. As article size decreases, the surface area to volume ratio increases. As the surface area of particle increases it causes greater interaction with solvent. The effect of particle size on solubility can be described by, [19]

$$\log \frac{S}{S_0} = \frac{2\ \gamma\ V}{2.303\ R\ T\ r}$$

Where, Where,

S is the solubility of infinitely large particles

S0 is the solubility of fine particles

V is molar volume

? is the surface tension of the solid

r is the radius of the fine particle

T absolute temp in degree kelvin

R universal gas constant

3.Molecular size:

Solubility affected by molecular size of particle. The solubility of the substance is decreased when molecules have higher molecular weight and higher molecular size because larger molecules are more difficult to surround with solvent molecules in order to solvate the substance. [20]

4. Temperature:

Solubility affected by temperature. If the solution process absorbs energy then the solubility will increase with increasing temperature. If the solution process releases energy then the solubility will decrease with increasing temperature. [21]

5. Pressure:

For solids and liquid solutes, solubility not affected by change in pressure but for gaseous solutes, solubility increases as pressure increases and decrease as pressure decrease[22].

TECHNIQUES TO OVERCOME POOR SOLUBITY

The description of a technology as **'solubility enhancing'** can be misleading, since although the phenomenon of super-saturation is real, the techniques used do not increase the solubility of insoluble compounds. More accurately, they present the drug in a form which is optimal to its absorption, given its solubility limitations. It is also important to be aware that water solubility also requires the specification of **temperature and pH**; many important drugs only exhibit aqueous solubility under certain physiological conditions, and these need to be met at the site of absorption [23].

The techniques that are used to overcome poor drug solubility are discussed below

I. Chemical Modifications:

1. Salt Formation
2. Co-crystallization
3. Co-solvency
4. Hydrotropic
5. Solublizing agent
6. Nanotechnology

II. Physical Modifications :

1. Particle size reduction

a. Micronization

b. Nanosuspension

2. Modification of the crystal habit

a.Polymorphs

b.Pseudopolymorphs

3.Complexation

a.Use of complexing agents

4.Solubilization by surfactants:

a.Microemulsions

b.Self microemulsifying drug delivery system

5.Drug dispersion in carriers

a.Solid dispersions

b.Solid solutions

I. CHEMICAL MODIFICATIONS

1.Salt Formation :

Salt formation is the most common and effective method of increase solubility and dissolution rates of acidic and basic drugs. Acidic or basic drug converted into salt having more solubility than respective drug. Ex. Aspirin**,** Theophylline, Barbiturates[24].

2. Co-crystallisation :

The new approach available for the enhancement of drug solubility is through the application of the co-crystals, it is also referred as molecular complexes. A Co-crystals may be defined as crystalline material that consist of two or more molecular (& electrical neutral) species held together by non-covalent forces. It can be prepared

by evaporation of a heteromeric solution or by grinding the components together or by sublimation, growth from the melt & slurry preparation. It is increasingly important as an alternative to salt formation, particularly for neutral compounds[25].

3. Co-solvent :

It is well-known that the addition of an organic cosolvent to water can dramatically change the solubility of drugs. Weak electrolytes and nonpolar molecules have poor water solubility and it can be improved by altering polarity of the solvent. Solvent used to increase solubility known as cosolvent. It is also commonly referred to as solvent blending[26].

4. Hydrotropy :

It designate to increase in solubility in water due to presence of large amount of additives. It improves solubility by complexation involving weak interaction between hydrophobic agents (Sodium benzoate, sodium alginate, urea) & solute. Ex. Sublimation of Theophylline with Sodium acetate & Sodium alginate[27].

5. Solublising Agents :

The solubility of poorly soluble drug can also be improved by various solubilizing materials. Ex. PEG 400 is improving the solubility of hydrochlorthiazide[28].

6. Nanotechnology Approaches :

Nanotechnology will be used to improve drugs that currently have poor solubility. Nanotechnology refers broadly to the study and use of materials and structures at the nanoscale level of approximately 100 nanometers (nm) or less. For many new chemical entities of very low solubility, oral bioavailability enhancement by micronisation is not sufficient because micronised product has very low effective surface area for dissolution and next step taken was nanonisation[29].

II. PHYSICAL MODIFICATIONS

1.Particle Size Reduction :

The techniques of size reduction using various milling processes are well established and these practices are a standard part of formulation development8. This can be done mainly by Micronization & Nanosuspension9. As particle size decreases, surface area of particle increases resulting in increase in solubility. Sometimes nanocrystallisation technique is also used for particle size reduction [30].

2.Modification of Crystal Habit:

Polymorphism is the ability of an element or compound to crystallize in more then one crystalline form. Different polymorphs of drugs are chemically identical, but they exhibit different physicochemical properties including solubility, melting point, density, texture, stability. Similarly amorphous form of drug is always more suited than crystalline form due to higher energy associated & increase in surface area. Order for dissolution of different solid forms of drug[31].

Amorphous >Metastable polymorph >Stable polymorph

3. Complexation :

Complexation is the association between two or more molecules to form a non bonded entity with a well defined stichiometry. Complexation relies on relatively weak forces such as London forces, hydrogen bonding and hydrophobic interactions7,12. Examples of complexaing agents are; chelates- EDTA, EGTA, molecular complexes- polymers, inclusion complexes cyclodextrins[32].

4. Solublisation By Surfactents :

Surfactants are molecules with distinct polar and nonpolar regions. Most surfactants consist of a hydrocarbon segment connected to a polar group. The polar group can be anionic, cationic, or nonionic. When small polar molecules are added they can accumulate in the hydrophobic core of the micelles[33]. This process of solubilization is very important in industrial and biological processes. The presence of

surfactants may lower the surface tension but increases solubility of drug within an organic solvent.

Methods for enhancing the Solubility & dissolution of class II drugs:

- Buffering the pH of microenvironment
- Use of salts of weak acids and weak bases
- Use of solvates and hydrates
- Use of selected polymorphic forms
- Complexation
- Prodrug approach
- Use of surfactants

POLYMORPHISM:

The relevance of polymorphism to the pharmaceutical industry is mainly to determine which form of a given API is the most stable for a particular pharmaceutical dosage form. Different crystalline polymorphs and solvates have different crystal packing, molecular conformation and lattice energy.

These result in differences in the physico-chemical properties of a drug, for instance density, hardness, tabletability, melting point, heat of fusion, solubility and dissolution rates. The differences in physical properties affect the preparation of drugs in dosage forms. Because of all these differences, it is important to understand the solid state properties of polymorphic forms, as well as understand polymorphism, in order to gain control over the crystallisation process. This knowledge helps enable the researcher to obtain a specific stable polymorphic form, suitable for a specific dosage form.

Polymorphism can be classified into two different categories, because of their differences in thermodynamic properties. *Enantiotropes* can reversibly transit between different polymorphs at a certain transition temperature below the melting point, while this is not possible for *monotropes.* [34]

SOLVATES:

It is important to note that crystalline solids exist in different forms and the three types of crystalline solids comprise polymorphs, solvates and hydrates.

Solvates are characterised as crystalline structures that contain solvent molecules, which cause significant differences in the physico-chemical properties of a drug. Solvates and crystalline solids have different molecular conformation and packing, hence different physical properties, such as melting points, dissolution rates, solubility, thermodynamic and kinetic properties. Solubility differences can impact on the absorption of these compounds.

Desolvated solvates are unsolvated compounds. These solvates have no distinctive crystalline form and therefore the molecules are not structured like their crystalline counterparts There are different ways for a solvent to interact with a crystalline solid:

- The solvent molecules can form weak interactions, namely van der Waals, dipole-dipole, or hydrogen bonding;
- The physical entrapment of the solvent in the growing crystal; and
- The adsorbing of solvent in a disordered manner in different regions of the crystal.

The different crystal faces of a substance have different affinities, therefore the amount of solvent or water absorbed in crystalline materials depends on their morphology and also on many other parameters. The solvent can also be physically entrapped in a crystal, called liquid inclusion. Large amounts of solvent may be adsorbed on the surface of the crystal, which can cause problems with grinding and granulation of these solvates. In an amorphous state the molecular entities are packed more closely, resulting in stronger intermolecular interactions and providing no space for solvent intake. Compounds can crystallise and bind with the solvent to form a solvate, in which case the solvent is a part of the crystalline structure Solvates can be divided into two categories, namely

- Stoichiometric solvates
- Nonstoichiometric solvates

Stoichiometric solvates are known as molecular compounds and the solvent is a part of the crystalline structure. The desolvation of a stoichiometric solvate usually results in a different crystalline structure, or leads to a disordered or amorphous state.

Nonstoichiometric solvates are inclusion compounds and the solvent is usually captured in channels of the crystalline structure. These solvates have large, awkward, crystal shapes, which cannot pack close together.

The ability of a solvate to form or to desolvate has a significant impact on the phase stability of these structures, because it is different for every form. The stability of solvates also depends on the temperatures and the partial pressure of the solvent. The formation of solvates is best when the crystallisation takes place at lower temperatures. The partial pressure of solvates also becomes practically zero for solvates with organic solvents, but not for hydrates, because of the atmospheric moisture. Stability depends on many factors, including the size of the crystals, crystal defects, dynamics of the atmosphere and the desolvation mechanism. To characterise and determine the stability of solvates, thermogravimetric analysis, like differential scanning calorimetry (DSC) can be used, because it analyses the thermal stability at dry atmospheric conditions, whilst it can be done at elevated humidity. The stability range of solvated and unsolvated forms can be determined through solubility studies at different temperatures. This is also used to determine the transition temperature between the different phases of the solvate .[34]

HYDRATES:

When a crystalline structure or compound is combined with water or a water element, this solvent is called a *hydrate*. It is easy for most pharmaceutical substances to form crystalline hydrates, since water is a small molecule that is capable of forming hydrogen bonds in multiple directions. This small molecule can also easily fill voids within the molecular packing of a solid. Water can therefore combine drug molecules in structured crystalline forms. It is important to note that the activity of water in a medium is the only reason why a hydrate structure will form. A monohydrate is a compound that contains one water molecule, whereas a dihydrate contains two water molecules. According to hydrates are characterised in three different categories:

Isolated site hydrates: Water molecules in this compound are isolated from others by combining with drug molecules, e.g. cephradine dihydrate;

Channel hydrates: Water molecules lie next to others and form channels through the crystal, e.g. ampicillin trihydrate.

Ion-associated hydrates: Metal ions are combined with water, e.g. calteridol calcium.

Phase changes can occur, for example when a hydrated compound converts into an amorphous phase, because of dehydration. This can cause a poorly soluble drug to convert into a compound that is much more soluble, whilst impacting negatively on the stability. Humidity, temperature and pressure can cause such phase changes.[35]

LITERATURE SURVEY

LITERATURE REVIEW

Ketan T.et al., Drug Solubility: Importance and Enhancement Techniques. Solubility, the phenomenon of dissolution of solute in solvent to give a homogenous system, is one of the important parameters to achieve desired concentration of drug in systemic circulation for desired (anticipated) pharmacological response. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as for the generic development. Various techniques are used for the enhancement of the solubility of poorly soluble drugs which include physical and chemical modifications of drug and other methods like particle size reduction, crystal engineering, salt formation, solid dispersion, use of surfactant, complexation, and so forth. Selection of solubility improving method depends on drug property, site of absorption, and required dosage form characteristics. .[36]

Mohini S.Patil1 et al., Solubility enhancement by various techniques: an overview. Solubility is not to be confused with the ability to dissolve or liquefy a substance, since this process may occur not only because of dissolution. But also because of a chemical reaction. Low aqueous solubility is the Major problem encountered with formulation development of new Chemical entities as well as for the generic development. More than 40% of new chemical entities developed in pharmaceutical industry are Lipophillic and fail to reach the market due to their poor water Solubility. The solubility behavior of drug is the major challenge for Formulation scientist. The present review is devoted to increase the Solubility of poorly water soluble drugs. .[37].

Marique Aucamp et al., Solution-mediated phase transformation of different roxithromycin solid-state forms: Implications on dissolution and solubility. The objective of this study was to describe the solid-state forms in which roxithromycin may exist and The significant influence of solution-mediated phase transformation on the dissolution and solubility Behavior of these forms. Roxithromycin may exist as: Form I (monohydrate), Form II (amorphous), Form III (anhydrate) and a mixture of Forms I and III. Form III and Mixture I/III have not been reported previously, Probably due to incomplete solid-state characterization. The Various forms differed

significantly in terms of dissolution profiles, which could have a marked influence On bioavailability and performance of the final dosage form. It was demonstrated that solvent replacement, During dissolution testing, masks the characteristic profile. Finally, we propose that peak dissolution concentrations Should be used to give a more exact indication of the aqueous solubility enhancement ratio obtained With metastable forms of API. .[38].

Amit Chaudhary et al., Enhancement of solubilization and bioavailability of poorly soluble drugs. By physical and chemical modifications: A recent review. The aim of this review was to improve the solubility and bioavailability of poorly soluble drugs by using various approaches like physical, chemical and others modifications or techniques. The solubility of a solute is the maximum quantity of solute that can Dissolve in a certain quantity of solvent or quantity of solution at a specified Temperature. Solubility is one of the important parameter to achieve desired Concentration of drug in systemic circulation for pharmacological response to be shown. Drug efficacy can be severely limited by poor aqueous solubility and some drugs also Show side effects due to their poor solubility. There are many techniques which are Used to enhance the aqueous solubility.[39].

Jinal N. Patel et al., Techniques to improve the solubility of poorly soluble drugs. A drug administered in solution form immediately available for absorption and efficiently absorbed than the same. Amount of drug administered in a tablet or capsule form. Solubility is a most important parameter for the oral Bioavailability of poorly soluble drugs. Dissolution of drug is the rate determining step for oral absorption of the Poorly water soluble drugs, which can subsequently affect the in vivo absorption of drug. It is now possible that to increase the solubility of poorly soluble drugs with the help of various techniques such as Physical method, Chemical method. Co-crystallisation, co-solvency solubilizing agents, molecular encapsulation with cyclodextrins, nanotechnology approaches and hydrotropy. [40].

Varun Raj Vemula et al., Solubility enhancement techniques Solubility is the phenomenon of dissolution of solid in liquid phase to give a homogenous system. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Water is the

solvent of choice for liquid pharmaceutical formulations. Most of drugs weakly acidic and weakly basic with poor aqueous solubility. Hence various techniques are used for the improvement of the solubility of poorly water-soluble drugs include micronization, chemical modification, ph adjustment, solid dispersion, complexation, co-solvency, micellar solubilization, hydrotropy etc. The purpose of this review article is to describe the techniques of solubilizaton for the attainment of effective absorption and improved bioavailability. [41].

Abhijit A. Et al., reviewed the Antisolvent Crystallization of Poorly Water Soluble Drugs. The enhancement in bioavailability of the drugs is One of the most important concerning aspects of the pharmaceutical industries. Preparation of nanoparticles or Microparticles of these drugs is the newest formulation strategies. An antisolvent crystallization technique is being used to prepare nanoparticles or microparticles for poorly water soluble drugs at research scale. This method has an ability to change the solid-state properties of pharmaceutical substances including the modification of crystal formation and particle size distributions. Therefore, various operating variables and their effect on the particle size of poorly water soluble drugs in an anti-solvent crystallization have been reviewed. [42].

Abhijit A et al.,The enhancement in bioavailability of the drugs is one of the most important concerning aspects of the pharmaceutical industries. Preparation of nanoparticles or microparticles of these drugs is the newest formulation strategies. The size and morphology of a drug are affecting several essential pharmaceutical properties. In general, the drug delivery system needs narrow particle size distribution with regular particle shape, particularly, an engineered drug particles to meet biopharmaceutical and processing needs. An antisolvent crystallization technique is being used to prepare nanoparticles or microparticles for poorly water soluble drugs at research scale. This method has an ability to change the solid-state properties of pharmaceutical substances including the modification of crystal formation and particle size distributions. Therefore, various operating variables and their effect on the particle size of poorly water soluble drugs in an anti-solvent crystallization have been reviewed. [43].

N.L. Prasanthi et al.., Formulated and evaluated roxithromycin tablets employing roxithromycin (ROX) solid dispersions.Dispersions of ROX in mannitol by different techniques like physical mixing, melting method, melt solvent method, kneading technique and common solvent method. The compressed tablets were evaluated for various tablet characteristics including dissolution rate and efficiency. Marked increase in the dissolution rate and efficiency was observed with tablets of dispersions in comparison to tablets formulated with physical mixtures and conventional tablets available commercially. Tablets prepared by dispersion of melt method have shown highest dissolution rate. Dissolution of ROX from these tablets obeyed first-order kinetics. [44].

Ayman A.et al.., Determined of Certain Macrolide Antibiotics in Pharmaceutical Preparations by Spectrophotometrically.A direct colorimetric method was described for the rapid, sensitive and accurate determination of certain macrolide antibiotics; roxithromycin (ROX), azithromycin (AZM), and clarithromycin (CLM) in bulk powder and in pharmaceutical preparations. The proposed method is based on reaction of the studied drugs with haematoxylin reagent in the presence of boric acid to give a reddish-violet chromogen λmax= 598 nm. [45].

Bryskier et al., reviewed of Roxithromycin antimicrobial activity. Roxithromycin is a semi-synthetic 14-membered-ring macrolide antibiotic in which the Erythronolide A lactone ring has been altered to prevent inactivation in the gastric milieu. The In-vitro activity of roxithromycin is well documented and similar to that of other macrolide Antibiotics. Roxithromycin is active against Gram-positive and Gram-negative cocci, Grampositive bacilli and some Gram-negative bacilli, but has no significant effect on the predominant faecal flora. It also displays good activity against atypical pathogens Like other macrolides, roxithromycin displays a significant postantibiotic effect which is dependent on the pathogens under study, the concentration of Roxithromycin and the duration of exposure. *In vivo*, roxithromycin is as effective or more Effective than other macrolides in a wide range of infections. [46].

Swapna.G et al., discussed about development and validation of new analytical Methods for the determination of roxithromycin in Bulk and

pharmaceutical formulations by uv-visible Spectrophotometry. In developing these methods, a systematic study of the effects of Various relevant parameters in the methods concerned were undertaken by varying one parameter at a time and controlling all other parameters to get maximum color development, minimum blank color, reproducibility and the reasonable period of stability of final colored Species formed. [46].

Chauhan Vanita et al., formulated an oro dispersible tablet (ODT) of the taste-masked Roxithromycin by incorporation of microspheres in the tablets. Microspheres of Roxithromycin were prepared by solvent evaporation method. The physical properties of prepared microspheres were evaluated with regard to yield, drug content, flow properties, particle size, in vitro drug release and taste. The average Size of microspheres was found to be satisfactory in terms of the size and size distribution. The odts prepared by direct compression method and evaluated for hardness, thickness, weight variation, friability, disintegration time, drug content, wetting time, in vitro disintegration, in vitro drug release and stability. [47].

Ms.Subhasri Mohapatrab et al., were prepared Dispersible tablets of Roxithromycin using a superdisintegrant such as Primogel powder, Kollidone powder, Crosscaramellose powder , and MCC in different concentration by direct compression method. Formulations were evaluated for the standard of dispersible tablets . It was observed that all the formulations were acceptable with reasonable limits of standard required for dispersible tablets. This study charecterise the most effective superdisintegrant. [48].

Abhishek Kumar Singh et al., formulated a FDT of the taste-masked Roxithromycin by incorporation of Excipients in the tablets. Method of Roxithromycin was prepared by solvent evaporation method. The optimized combinations were subjected to FT-IR and while dissolution, and accelerated stability studies were performed on their formulations. The physical properties were evaluated with regard to yield, drug content, flow properties, particle size, in vitro drug release and taste. The average size of microspheres was found to be satisfactory in terms of the size and size distribution. The fdts Prepared by direct compression method and evaluated for hardness, thickness, weight variation, friability, disintegration time, drug

content, wetting time, in vitro disintegration, in vitro drug release and stability. Result and discussion simulated salivary fluid (ph 6.8) and sufficient flow properties was shown in the drug: polymer ratio. [49].

Raiyani rushang.c et al., Formulated and evaluated of fast disintegrating tablet of roxithromycin. The calibration curve of Roxithromycin was prepared in phosphate buffer ph 6.0 follow the beer lamberts law between the different Concentration ranges at λmax 205 nm. Formulation parameters like solubility study, melting point determination, water content, drug exstudy at different temperature were carried out. Different preformulation excipients interactionout. Data obtained from above pre-formulation study concluded that there is no interaction between drug and involved excipients in this project study. The tablets were evaluated for thickness, hardness, friability, weight variation, wetting time, water absorption, drug content, disintegration time and *in vitro* dissolution studies. [50].

Nief Rahman Ahmed et al., developed New spectrophotometric determination of roxithromycin in pharmaceutical preparations and environmental samples. A new, simple, selective, sensitive and accurate direct spectrophotometric method has been developed for the determination of roxithromycin in pure form , pharmaceutical preparations and environmental water samples. The method was based on the reaction of roxithromycin with concentrated sulfuric acid to form red color product having absorption maxima at 485nm. [51].

B.N. Suhagia et al., developed Spectrophotometric method for determination of roxithromycin in its pharmaceutical dosage forms. In the proposed method, roxithromycin is oxidized with potassium permanganate to liberate formaldehyde, which is determined *in situ* using acetyl acetone in the presence of ammonium acetate to give a yellow-coloured chromogen with absorption maxima at 412 nm. The method is found to be linear in the concentration range of 10-75 µg/ml with regression coefficient of 0.9987. [52].

Sandhya Bhimrao Lahane et al., developed new Analytical Method for Macrolide Antibiotic Macrolide antibiotics, mostly derivatived from erythromycin, are a class of antimicrobial compounds widely used against infectious diseases. The quantification of macrolide antibiotic in tablet formulation for routine quality control

analysis using transmission Fourier Transform Infrared (FT-IR) spectroscopy. A number of analytical techniques such as ultraviolet (UV), high performance liquid chromatography(HPLC),capillary electrophoresis, various electrochemical detections, near infrared (NIR) and liquid chromatography/mass spectrometry (LC/ MS) have been applied for the determination and qualitative analysis of macrolide antibiotics in raw materials, dosage forms and biological samples. [53].

A.S Mundada et al., Formulation and evaluation of dispersible taste masked tablet of roxithromycin. Roxithromycin is a broad spectrum, semisynthetic macrolide antibiotic, having bitter taste. The complexes were evaluated for bulk density, angle of repose, taste masking, and *in vitro* drug release. *In vitro* drug release studies showed more than 80% drug release from the optimized formulation within 30 min. Amberlite IRP64 was found to be better complexing agent for masking the bitter taste of roxithromycin.[54]

Praveen Kumar et al., A Study on Solubility Enhancement Methods for Poorly Water Soluble Drugs. It is generally recognized that poor solubility is one of the most frequently encountered difficulties in the field of pharmaceutics. Low solubility and subsequent unsatisfactory dissolution rate often compromise oral bioavailability. However, poorly water-soluble drugs, when administered orally, have been shown to be slowly and unpredictably absorbed since their bioavailability is largely dependent on the dissolution process in gastrointestinal tract. This article demonstrates the various methods used to increase dissolution rates, preparation techniques of solid dispersion, and characterization methods of the solid dispersion.[55]

C.M Bhaskar Reddy et al., developed UV spectrophotometric method for the estimation of Roxithromycin in bulk and tablet dosage form. Roxithromycin shows maximum absorbance at 420nm in presence of solvent Deionised Water and phosphate buffer of ph 7.4. The Beer's law is obeyed in the concentration range of 20-70 µg/ ml for this drug. The graph of the drug shows a straight line with correlation coefficient of 0 .9840. The assay method of the drug was validated by accuracy and precision of the proposed method. The results are validated as per the directions of International conference on Harmonization.[56]

G. V Subbareddy et al.,Development, validation and application of UV spectrophotometric method for the determination of roxithromycin in bulk and pharmaceutical dosage form. Roxithromycin is a semi-synthetic macrolide antibiotic. It is used to treat respiratory tract, urinary and soft tissue infections. The present research work discussed the development of a simple, sensitive, rapid, accurate, precise and economical UV Spectrophotometric method for the evaluation of Roxithromycin in bulk and pharmaceutical dosage form which is based on the measurement of absorption maxima at 420 nm.[57]

AIM AND OBJECTIVES

AIM AND OBJECTIVE

AIM OF THE STUDY:

Roxithromycin is a BCS Class II /IV drug belonging to macrolide antibiotic used in the treatment of a broad variety of infections, of which respiratory tract infections are the primary indication. But Roxithromycin has only 50% oral bioavailability, due to its poor aqueous solubility, which limits its potential for optimal drug delivery and therapeutic effect. Its poor solubility is thus an obstacle in formulation development.

So it is more cost effective to chemically re-design a molecule than to move through the whole development process, it is crucial to develop a formulation that overcomes problems of insolubility. The aim of this study to enhance the solubility of Roxithromycin by using its solvates.

OBJECTIVE OF THE STUDY:

The objectives of this study to enhance the solubility and Dissolution by

- To Prepare Roxithromycin solvates using Choloroform and Ethanol as solvents
- To characterise the different forms prepared;
- To evaluate the Solvated form forms on their solubility and Dissolution
- To find the suitability of Solvated form in Pharmaceutical Formulation.

PLAN OF WORK

PLAN OF WORK

The present work carried out to solubility and dissolution enhancement of roxithromycin which is having low bioavailability due to its poor aqueous solubility. So study was carried out to enhance the Solubility and dissolution of Roxithromycin in the following steps

1. Literature survey
2. Procurement of drug and Chemicals
3. Preformulation of Roxithromycin
4. Preparation of Roxithromycin Solvates
5. Characterisation of Roxithromycin Solvates
6. Formulation of Roxithromycin Solvates

MATERIALS AND METHODS

MATERIALS AND METHODS

LIST OF EQUIPMENTS:

S.NO	NAME OF EQUIPMENTS	MANUFACTURER
01.	Digital balance	SHIMADZC ELB 300
02.	UV- visible spectrometer	SHIMADZC UV -1700
03.	FTIR	SHIMADZU
04.	XRD	BRUKER ECO D8
05.	SEM Analyser	ZEISS-5200 SEM
06.	Hot air oven	ELCON
07.	Magnetic stirrer	REMI
08.	Dissolution Apparatus	LABINDIA
09.	Disintegration apparatus	INCO
10.	Tablet Punching Machine	REMEK
11.	Hardness Tester	PFIZER
12	Friability Apparatus	INCO

Table no:4

LIST OF MATERIALS

S.NO	MATERIALS	MANUFACTURER
01.	Roxthiromycin	GIFT sample from Madras Pharmaceuticals
02.	Ethanol	Sisco research laboratory
03.	Chloroform	Sisco research laboratory
04.	Microcrystalline Cellulose	GIFT sample from Microlabs
05.	Talc	Sd fine Chemicals,Mumbai
06.	Sodium Starch Glycolate	Sd fine Chemicals,Mumbai
07.	Magnesium Sterate	GIFT sample from Microlabs

Table no:5

DRUG PROFILE

DRUG PROFILE

ROXITHROMYCIN[58]:

Roxithromycin is a semi-synthetic macrolide antibiotic. It is used to treat respiratory tract, urinary and soft tissue infections. Roxithromycin is derived from erythromycin, containing the same 14-membered lactone ring.

It acts on gram-positive bacteria and gram-negative bacteria. It is used to treat respiratory tract, urinary and soft tissue infections. Roxithromycin is derived from erythromycin, containing the same 14-membered lactone ring. However, an N-oxime side chain is attached to the lactone ring. It is also currently undergoing clinical trials for the treatment of male-pattern hair loss.

Roxithromycin is available under several brandnames, for example, Xthrocin, Roxl-150, Roxo, Surlid, Rulide, Biaxsig, Roxar, Roximycin, Roxomycin, Rulid, Tirabicin and Coroxin. Roxithromycin is not available in the United States. Roxithromycin has also been tested to possess antimalarial activity.

Roxithromycin prevents bacteria from growing, by interfering with their protein synthesis. Roxithromycin binds to the subunit 50S of the bacterial ribosome, and thus inhibits the translocation of peptides. Roxithromycin has similar antimicrobial spectrum as erythromycin, but is more effective against certain gram-negative bacteria, particularly *Legionella pneumophila* Roxithromycin has fewer interactions than erythromycin as it has a lower affinity for cytochrome P450 Roxithromycin does not interact with hormonal contraceptives, prednisolone, carbamazepine, ranitidine or antacids.

Rroxithromcin is 150 mg twice in a day, 30 minutes before meals or 2 hours after. For children, it is 2.5 - 5.0 mg/kg of body weight, given in two divided doses per day.

It is used in respiratory tract infections like pharyngitis, pneumonia, chronic bronchitis and bronchopneumonia.

Chemical names: (3*R*, 4*S*, 5*S*, 6*R*, 7*R*, 9*R*, 11*S*, 12*R*, 13*S*, 14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-O-methyl-α-L-*ribo*-hexopyranosyl)oxy]-14-ethyl-7,12,13-

trihydroxy-10-[(*E*)-[(2-methoxyethoxy)-methoxy]imino]-3,5,7,9,11,13,-hexamethyl-6-[(3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl)oxy]-oxacyclotetradecan-2-one.

Structural of roxithromycin:

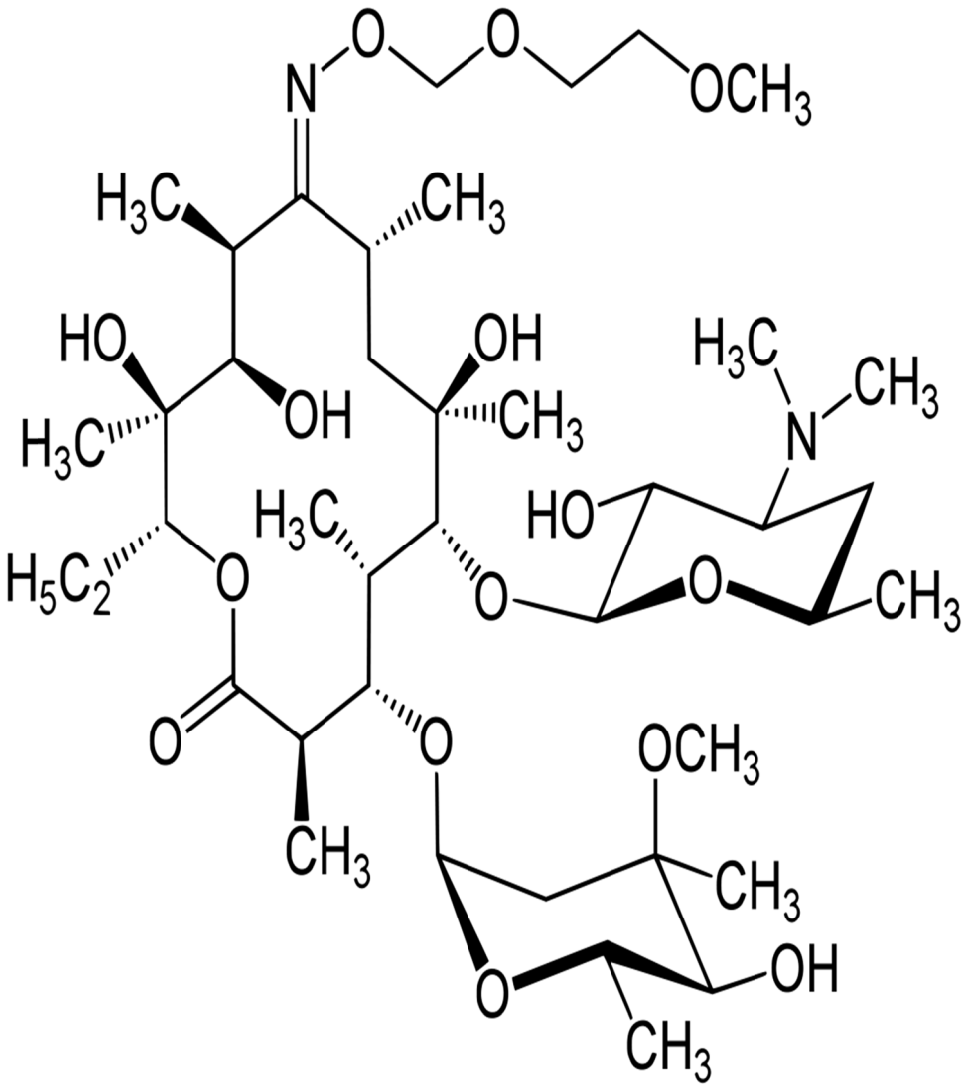


Figure no :4

Molecular formula: C41H76N2O15.

Molecular weight: 837.07

Appearance and colour: Roxithromycin is a white, crystalline powder

Boiling Point*:* 864.7 °C at 760 mmHg.

Melting point: 115- 120 ^{0}C.

MECHANISM OF ACTION:

Roxithromycin prevents bacteria from growing, by interfering with their protein synthesis. Roxithromycin binds to the subunit 50S of the bacterial ribosome, and thus inhibits the translocation of peptides. Roxithromycin has similar antimicrobial spectrum as erythromycin, but is more effective against certain gram-negative bacteria.

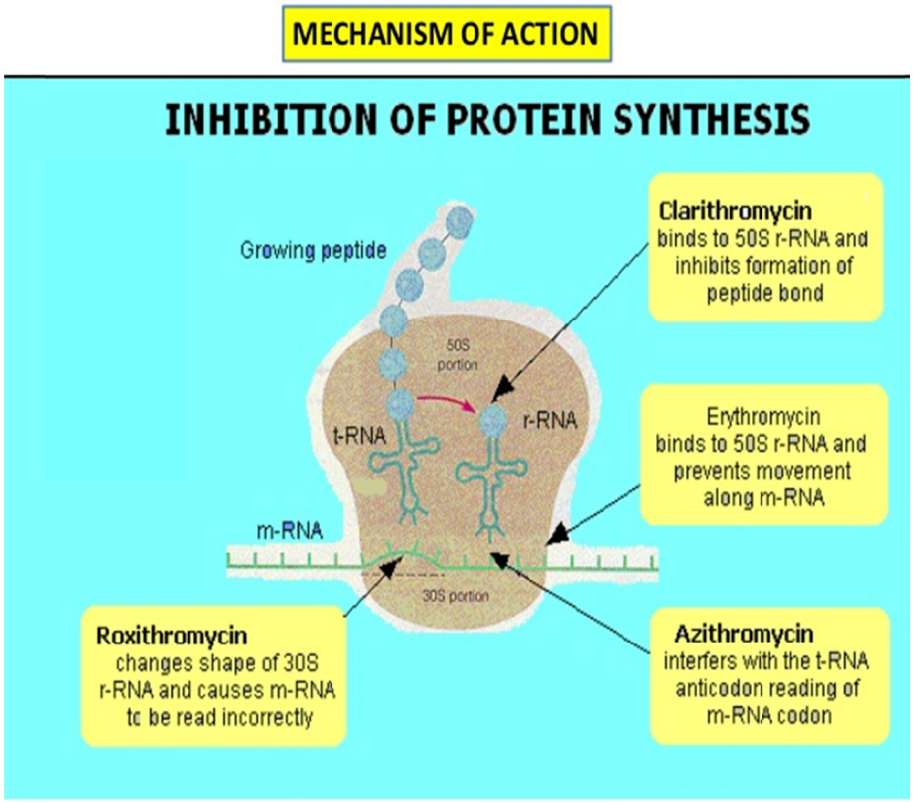


Figure no:5

DESCRIPTION:

Roxithromycin is a semi-synthetic macrolide antibiotic. It is a white crystalline powder. Roxithromycin is very slightly soluble in water, freely soluble in acetone, in alcohol and in methylene chloride. It is slightly soluble in dilute hydrochloric acid.

Dosage:

Adult: *PO* 150 mg twice daily or 300 mg once daily for 5-10 days.

Administration:

Should be taken on an empty stomach. Take at least 15 min before meals.

Pharmacodynamics:

Macrolides are considered time-dependent antibiotics.

Pharmacokinetics:

Cmax: 6.8mg/L

Half- life: 8-13 hours

Bioavailability: 72-85%

Adverse Effects:

- Gastrointestinal: abdominal cramps, nausea, diarrhea, anorexia, pancreatitis
- Genitourinary: vulvovaginal candidiasis, renal failure
- Cardiovascular System: prolongation of QT interval
- Hepatic: hepatotoxicity, jaundice
- Hematologic: eosinophilia, thrombocytosis, lymphopenia
- Central Nervous System: headache, fatigue
- Endocrine/Metabolic: hyperglycemia
- Dermatologic: itching, nail discoloratiom

Warnings and precautions :

Caution should be exercised in patients with history of liver impairment, abnormal heart rhythm, any allergy, who are taking other medications, during pregnancyand breastfeeding. Monitor liver function regularly while taking this medication.

Avoid long-term use of this medication; otherwise it may cause liver damage.

Other Precautions :

Avoid excess dosage.

Storage Conditions :

Store it at room temperature.

Uses:

- acute pharyngitis (sore throat and discomfort when swallowing)
- tonsillitis.
- sinusitis.
- acute bronchitis (infection of the bronchi causing coughing)
- pneumonia (lung infection characterised by fever, malaise, headache).

EXCIPIENT PROFILE

ETHANOL [59]

Synonyms:

1-Hydroxyethane

Alcohol

Alcohol (ethyl)

Alcohol anhydrous

MOLECULAR FORMULA :

C_2H_6O

ETHANOL STRUCTURE:

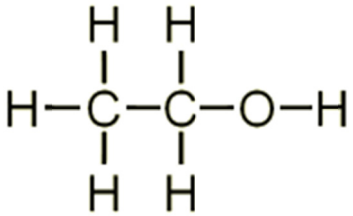


Figure no :6

Weight

Average: 46.0684

Description :

A clear, colorless liquid rapidly absorbed from the gastrointestinal tract and distributed throughout the body

Uses:

Solvent and preservative in pharmaceutical preparations as well as serving as the primary ingredient in alcoholic beverages.

CHLOROFORM [59]

Chloroform is a commonly used laboratory solvent. It was previously used as an anesthetic.

Chemical Names:

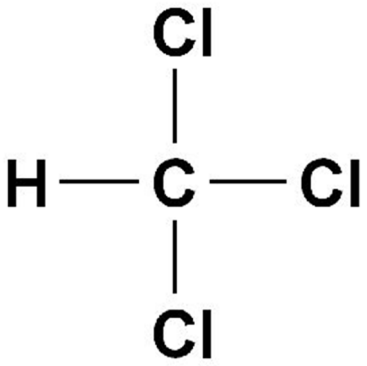
Trichloroform

Molecular Formula:

$CHCl_3$

Structure of chloroform:

Figure no :7



Molecular Weight:

119.369 g/mol

Description:

Chloroform is a clear colorless liquid with a characteristic odor.

Solubility:

Miscible with alcohol, ether, benzene, carbon tetrachloride, fixed and volatile oils; highly soluble in water.

Density

1.564 g/cm^3 (−20 °C)
1.489 g/cm^3 (25 °C)
1.394 g/cm^3 (60 °C)

Melting point

−63.5 °C (−82.3 °F; 209.7 K)

Boiling point

61.15 °C (142.07 °F; 334.30 K)

decomposes at 450 °C

Uses:

Analgesic

Solvent etc.

MICROCRYSTALIN CELLULOSE[59]

Microcrystalline cellulose is a term for refined wood pulp and is used as a texturizer, an anti-caking agent, a fat substitute, an emulsifier, an extender, and a bulking agent in food production. The most common form is used in vitamin supplements or tablets.

Chemical name:

cellulose gel

Chemical formula:

$(C_6H_{10}O_5)_n$

Sructure of microcrystalin cellulose:

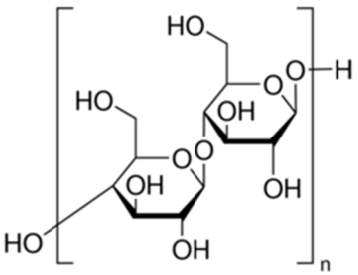


Figure no 8 :

Description:

Fine, white or almost white, odourless, free flowing crystalline powder

Solubility*:*

Insoluble in water, ethanol, ether and dilute mineral acids. Slightly soluble in sodium hydroxide solution

Loss on drying:

Not more than 7.0% (105 °, 3h)

pH

5.0 - 7.5 Shake 5 g of the sample with 40 ml of water for 20 min and centrifuge. Use the supernatant for pH determination

Functional uses:

Emulsifier, stabilizer, anticaking and dispersing agent.

SODIUM STARCH GLYCOLATE

Sodium starch glycolate is used as a pharmaceutical grade dissolution excipient for tablets and capsules. **Sodium starch glycolate** absorbs water rapidly, resulting in swelling which leads to rapid disintegration of tablets and granules. It is used as a disintegrant, a suspending agent and as a gelling agent.

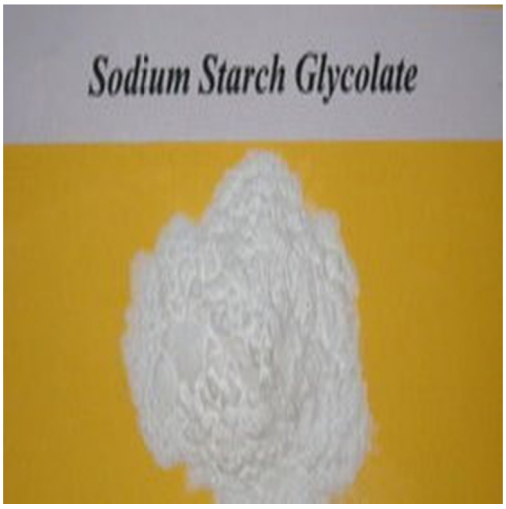


Figure no 9:

Synonyms :

Carboxymethyl starch, sodium salt; carboxymethylamylum natricum; Explosol; Explotab; Glycolys; Primojel; starch carboxymethyl ether, sodium salt.

Chemical Name:

Sodium carboxymethyl starch

Description :

Sodium starch glycolate is a white or almost white free-flowing very hygroscopic powder

Melting point:

Does not melt, but chars at approximately 2008C.

Functional Category:

Tablet and capsule disintegrant.

TALC [59]

Talc is a clay mineral composed of hydrated magnesium silicate. Naturally occuring form of hydrous magnesium silicate containing varying proportions of such associated minerals as alpha-quartz, calcite, chlorite, dolomite, kaolin, magnesite, and phlogopite. Talc derived from deposits that are known to contain associated asbestos is not food grade.

Formula: $H_2Mg_3(SiO_3)_4$ or $Mg_3Si_4O_{10}(OH)_2$.

Structure of Talc:

Figure no 10:

Transparency: Transparent, Translucent

Synonyms: Talcum

Description:

Odourless, very fine, white or grayish white, crystalline powder. It is unctuous, adheres readily to the skin, and is free from grittiness.

Functional uses:

Anticaking agent, filtering aid, coating agent, lubricating and release agent, surface-finishing agent, texturizing agent, filter aid, dusting powde**r.**

Solubility: Insoluble in water and ethanol

Density:

2.58 - 2.83 g/cm^3 (Measured) 2.78 g/cm^3

Lustre:

Sub-Vitreous, Resinous, Waxy, Greasy, Pearly

Thermal Behaviour:

Stable to about 900° Celsius.

Health Risks:

talcum powders may have small amounts of amphibole contamination.

Industrial Uses:

Filler in paints, rubber. In cosmetics and as a lubricating dusting powder.

PREPARATION OF REAGENTS AND SOLUTION

PREPARATION OF 0.1N HCl :

8.5ml of hydrochloric acid and add with 1000 ml of water is makeup volumetric flask.ee

PREPARATION OF PHOSPHATE BUFFER pH 6:

6.8 gm potassium dihydrogen phosphate and 1000ml of water adjust the pH 6 by using sodium hydroxide.

PREPARATION OF STANDARD STOCK SOLUTION AND CALIBRATION CURVE:

Standard stock solution prepared by 10 mg of Roxithromycin as dissolving in 10 ml of 0.1N HCL in volumetric flask than further 1 ml is dissolved in 100 ml to get concentration of 10µg/ml. The aliquots of 0.5 to 3 ml of standard stock solution were transferred into series of 10ml volumetric flask and made up to mark with 0.1N HCL to reach the concentration range of 0.5µg/ml to 3µg/ml respectively. A graph of absorbance versus concentration of the solution was recorded with help of UV spectrophotometer at 205nm.

Table no: 6 CALIBRATION CURVE OF ROXITHROMYCIN

S.NO	CONCENTRATION (µg/ml)	ABSORBANCE
01.	0.5	0.106
02.	1	0.210
03.	1.5	0.312
04.	2	0.405
05.	2.5	0.5
06.	3	0.589

Calibration Curve of Roxitromycin

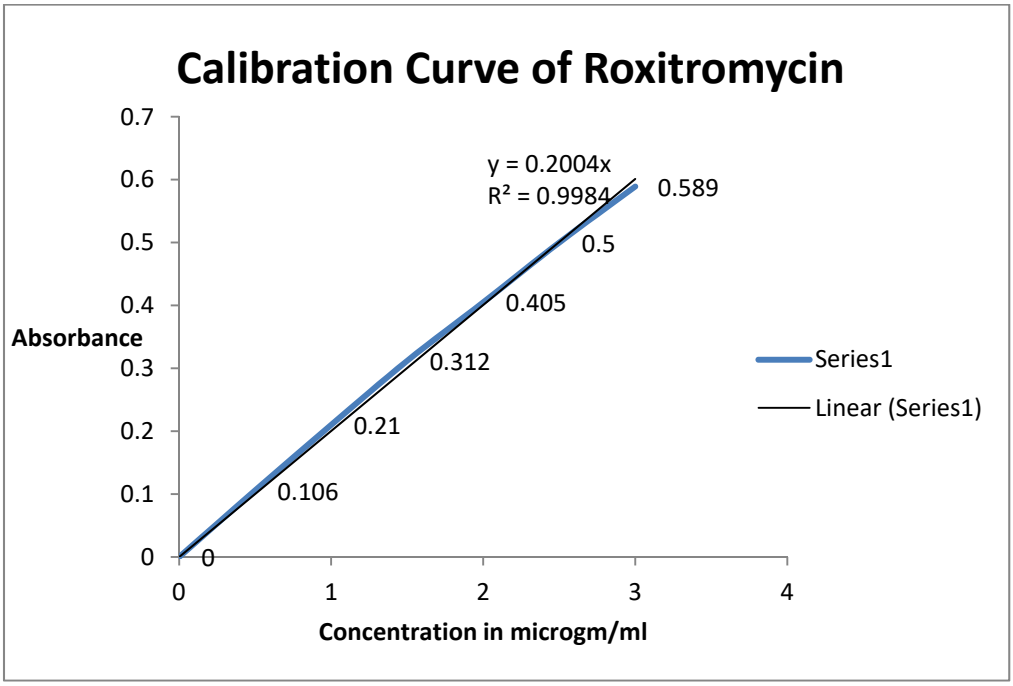


Figure No:11

EXPERIMENTAL INVESTIGATIONS

EXPERIMENTAL INVESTIGATIONS

Preformulation studies

Preformulation testing is an investigation n of physical and chemical properties of drug substances alone and when combined with excipients.It is the first step in the rational development of dosage forms. The overall objective of preformulation testing is to generate information useful to the formulation in developing stable and bioavailable dosage forms. The use of preformulation parameters maximizes the change in formulating an acceptable, safe, efficacious and stable product.

Identification of drug:

The identification of drug was done by FTIR spectroscopy. Roxithromycin mixed with suitable quantity of potassium bromide. About 100mg of this mixture was compressed to form a transparent pellet using a hydrallic press at 10 tons pressure. It was scanned from 4000 to 500cm^{-1} in a FTIR Spectrophotometer.The FTIR spectrum of pure drug Roxithromycin is shown in Figure.

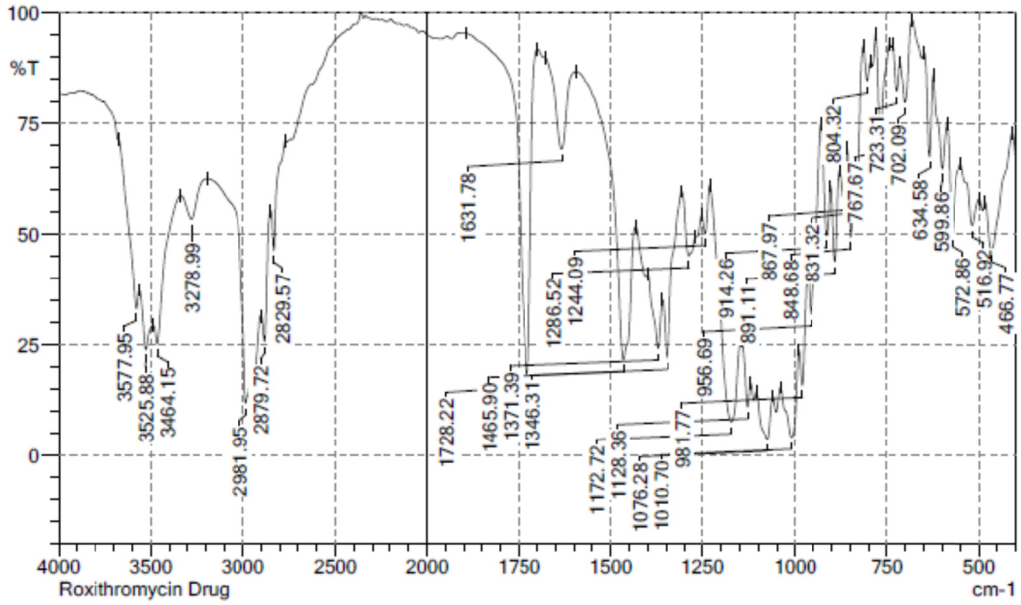


Figure No 12: IDENTIFICATION OF DRUG

Physical Characteristics of Drug:

Solubility Studies:

100 mg of Roxithromycin dissolved in 100 ml of each distilled water ,0.1 N HCI and phosphate buffer (pH 6) in a separate beaker and kept it in a magnetic stirrer at 50 rpm for 24 hours in room temperature. After 24 hours the concentration of the filtered Samples were determined spectro photometrically at 205 nm at UV visible Spectrophotometer. The Procedure was repeated at three times. The Solubility results were tabulated based on the % concentration of drugs soluble in the given solvent given below

% Concentration of Drug in given solution	Distilled water	0.1 N Hcl	Phosphate Buffer pH 6
1 Test	8.1	32.12	67.85
2 Test	7.23	41.17	69.12
3 Test	7.45	40.82	69.3
Average	7.59	38.03	68.75

Table no 7: Determination of bulk density and tapped density

An accurately weighed quantity of the powder (W) was carefully poured into the graduated cylinder and the volume (Vo) was measured. Then the graduated cylinder was closed with lid, set into the density determination apparatus (bulk density apparatus). The density apparatus was set for 100 taps and after that, the volume (Vf) was measured and continued operation till the two consecutive readings were equal. The bulk density, and tapped density were calculated using the following formulas

Bulk density = W / Vo

Tapped density = W / Vf

Where, W = weight of the powder,

V_O = initial volume

Vf = final volume

Compressibility index

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. A material having values of less than 20 to 30% is defined as the free flowing material.

$$CI = \frac{100\ (Vo - Vf)}{V0}$$

Hausner's ratio

The hausner's ratio is the ratio between tapped density to bulk density. It indicates the value for flowability.If the value less than 1.25 flows is excellent. If the value is greater than 1.25 it indicates poor flow. It requires 0.2%w/w of Glidant to improve the flowability.

Hausner's Ratio = Tapped Density / Bulk Density

Angle of Repose:

Angle of Repose (Φ) is the maximum angle between the surface of a pile of powder and horizontal plane. It is usually determined by Fixed Funnel Method and is the measure of the flowability of powder/granules.

$\Phi = \tan^{-1} (h / r)$

Where,

h = height of heap of pile r = radius of base of pile

Table no 8: angle of repose and flow property of powder drug

S.NO	Angle Of Repose	Flow Property
1.	Less than 25˚	Excellent flow
2.	25˚ to 30˚	Good
3.	30˚ to 40˚	Possible flow
4.	greater than 40˚	Very poor

LOSS ON DRYING

Place the bottle in the oven, remove the stopper (placing it nearby), dry under the specified conditions, stopper again, take the bottle out of the oven, and weigh it again. If heated, unless otherwise specified, allow to cool it in desiccators, and weigh it accurately. If the powder melts at a temperature lower than the specified drying temperature, dry it at a temperature 105 °C ± 2 °C lower than the melting temperature for 1 to 2 hours, and dry it under the specified conditions.

Loss on drying = Initial weight of the drug – Final weight of the drug X 100

Initial weight of the drug

Sl.No	Parameters	Roxithromycin
1.	Bulk density (g/ml)	0.3844
2.	Tap density (g/ml)	0.4908
3.	Compressibility Index	21.67
4.	Hausner's Ratio	1.2767
5.	Angle of repose(°)	36
6.	Loss on drying (%)	2.2

Table no:9 Physical parameter of Roxithromycin

Drug Excipients Compatibility Studies:

The compatibility of Drug and Excipient were done by FTIR spectroscopy by scanned from 4000 to 500cm-1 in a FTIR Spectrophotometer. Physical mixture Roxithromycin and excipients were scanned from 4000 to 500cm-1 in a FTIR Spectrophotometer. FTIR spectra of Physical Mixture was given below.

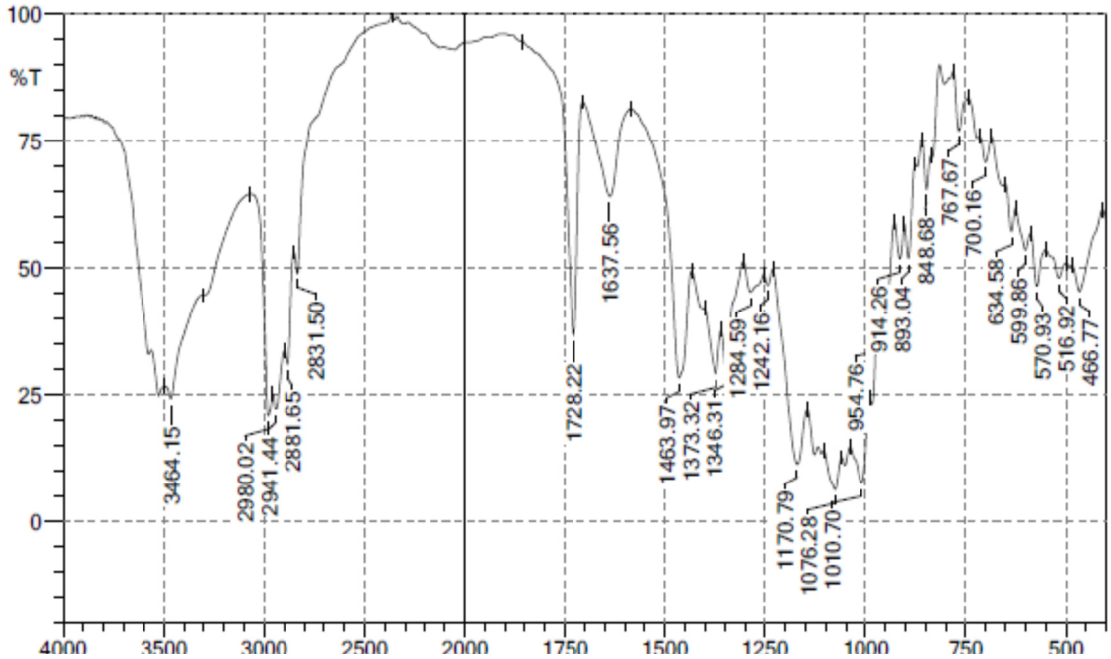


Figure no13: Drug Excipients Compatibility Studies

Preparation of Roxithromycin Solvates:

The solvate of roxithromycin was prepared by recrystallization of the raw material from Solvent (Chloroform ,Ethanol). Approximately 5 g of roxithromycin was added to 50 mL of Solvent while stirring continuously and heating the solution to approximately 60°C in a magnetic stirrer for 4 hours. After slow evaporation of the Solvent, a dense mass was obtained. This mass was dry but tend to stick to the surfaces of containers. The desolvated solid was prepared by placing the Roxithromycin solvate in a Dessicator at room temperature for 48 hrs. Then it was triturated and stored in airtight container.

Material	Formulation Code
Roxithromycin	F 1
Roxithromycin Choloroform Solvate	F2
Roxithromycin Ethanol Solvate	F 3

Table No10: Formulation Code for Roxithromycin Solvate

Characterization of Roxithromycin Solvates:

The prepared roxithromycin solvates were characterized by the following re analytical methods were used to differentiate their crystalline nature and its role in solubility.

FTIR STUDIES:

The structural changes due to drug solvent interaction drug was done by FTIR spectroscopy. Roxithromycin and Solvates were scanned from 4000 to 500cm-1 in a FTIR Spectrophotometer. FTIR spectra of F1 ,F2,F3 were given below

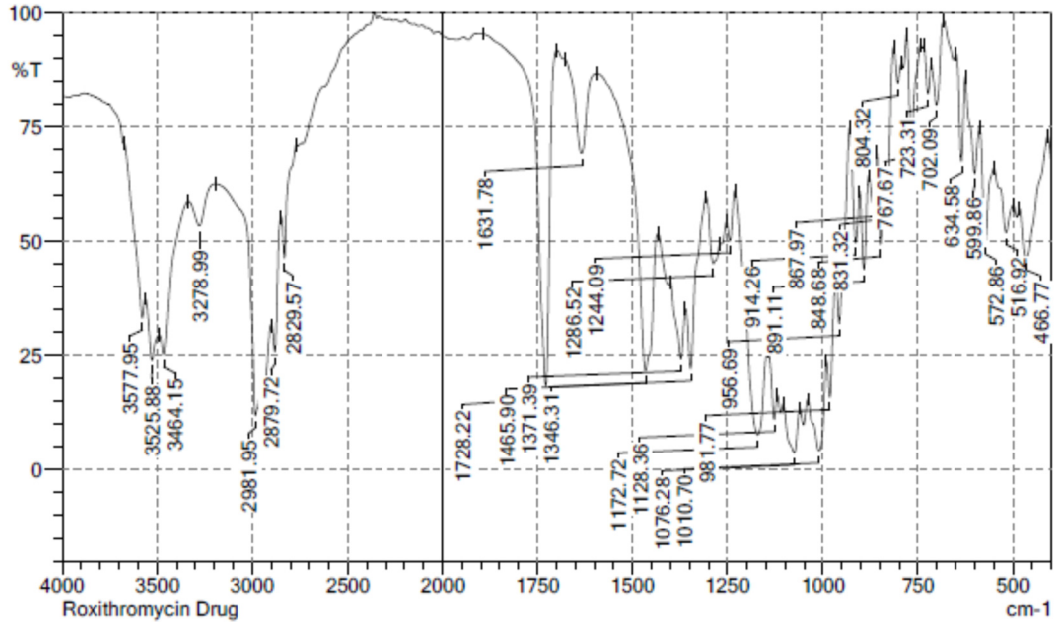


Figure no 14: FTIR Studies of Roxithromycin

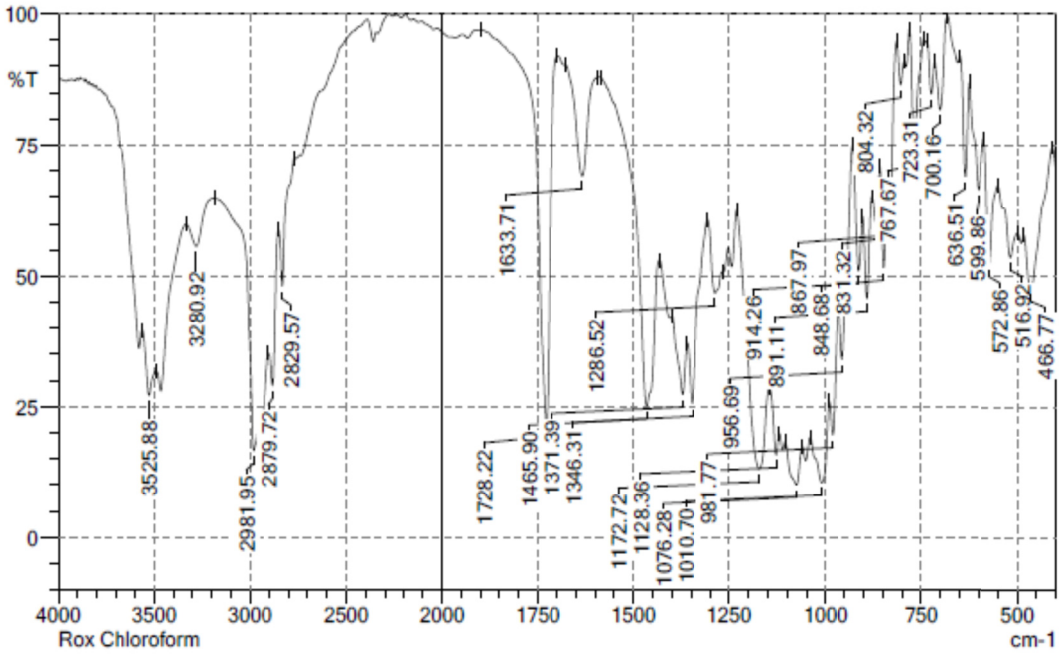


Figure No 15: FTIR Studies of Roxithromycin chloroform Solvate

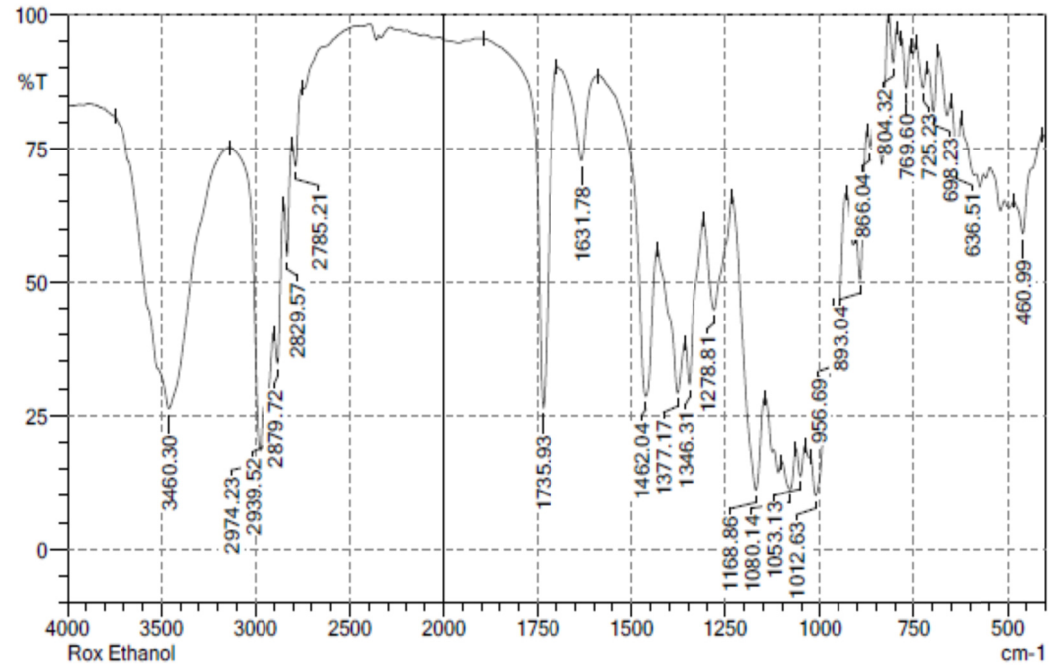


Figure No 16: FTIR Studies of Roxithromycin Ethanol Solvate

X-ray powder diffraction (XRPD) STUDIES:

The XRD studies for analyzing structural of roxithromycin and choloform ,ethanol crystals. The samples were placed in sample cell and spread evenly. The sample cell was placed in X- ray powder diffractometer (BRUKER ECO D8). The X-ray powder diffraction patterns of the Roxithromycin and its solvates were given below

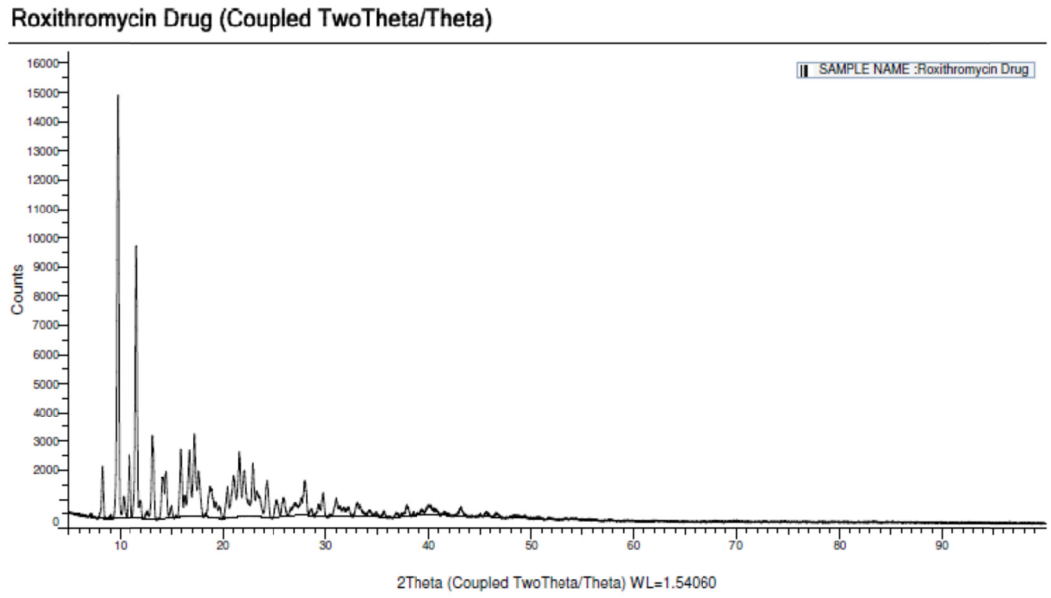


Figure No 17: XRPD Studies of Roxithromycin

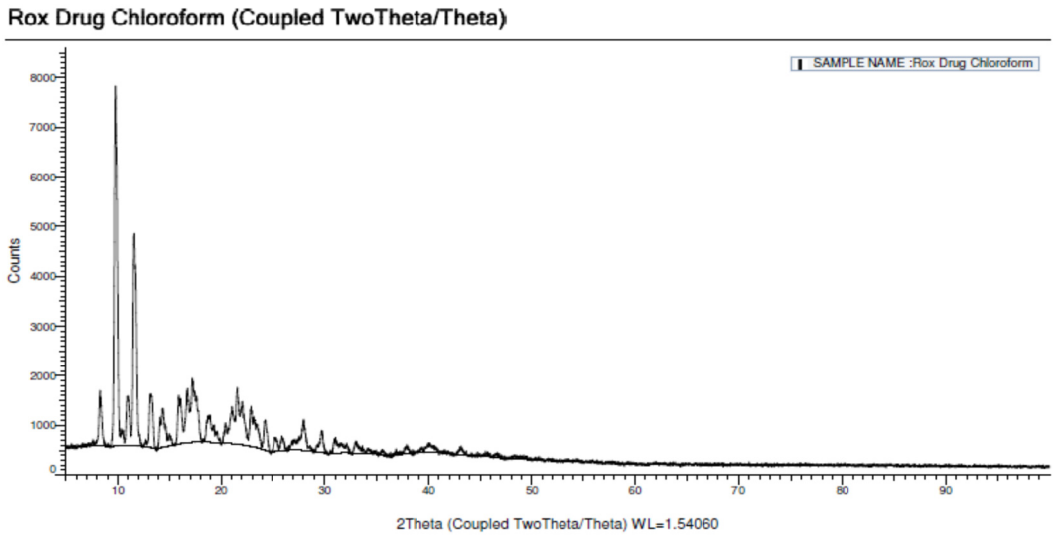


Figure No18: XRPD Studies of Roxithromycin chloroform solvate

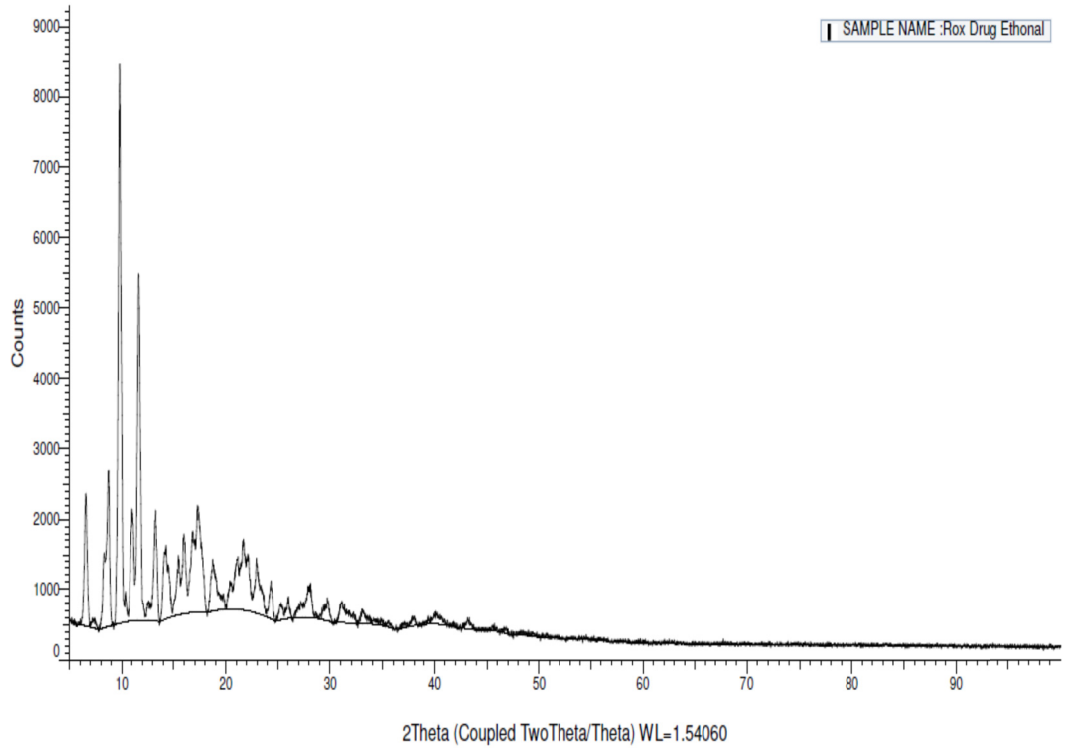


Figure No19: Formulation Code F3 of XRPD Studies of Roxithromycin Ethanol Solvate

SEM Analysis: [SCANNING ELECTRON MICROSCOPE]

SEM analysis used to measure the particle size and shape. The morphological appearance of the electrospun fiber and that fiber were investigated by ZEISS- 5200 scanning electron microscope[SEM], operating at an acceleration voltage of 20KV. For each sample, the average diameter of the individual fibers was measured from multiple SEM images at the magnification of 2.0KX by semaphore 4.0 software. The result of each sample was reported as an average value measurements. A Lloyd LRX universal tester was used to determine the mechanical integrity of some of the as – spun fibers. The gauge length and the crosshead speed were 10µm per minute, respectively. Scanning electron microscopy (SEM) images of the Roxithromycin, the chloroform solvate and Ethanol Solvate were given below.

Figure No20: SEM Studies of Roxithromycin F1

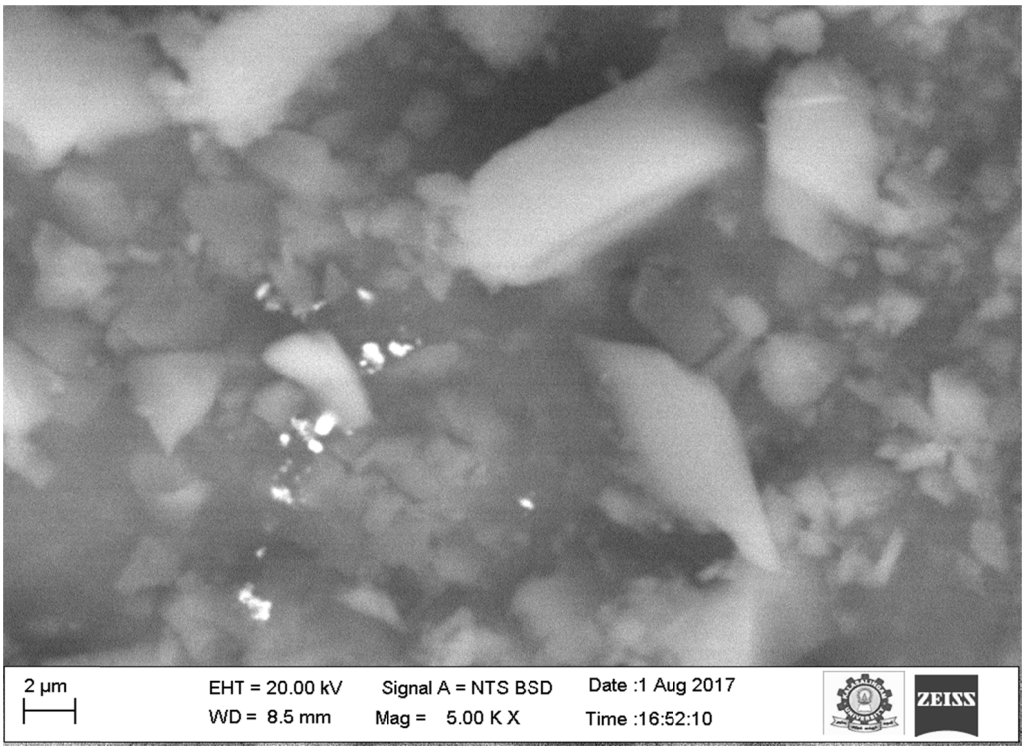


Figure no 21: SEM Studies of Roxithromycin chloroform Solvate

Figure no 22 : SEM Studies of Roxithromycin Ethanol Solvate

Aqueous Solubility Studies:

Aqueous solubility studies were carried out by adding excess of drug (F1,F2,F3) 100 mg in 100 ml of distilled water .They were were continuously stirred on an electromagnetic stirrer with at 37 °C and 100 rpm for 48 hrs. Then filtered ,suitably diluted and analyzed, spectrophotometrically (UV-1700, UV/Vis spectrophotometer, Shimadzu, Japan), for the dissolved drug at 205 nm.

Table no12: Aqueous solubility studies

S.No	µg/ml in solution		
	F1	F2	F3
1	1.08	6.38	5.12

DISSOLUTION STUDIES:

In-vitro Dissolution studies were performed using USP Type II dissolution paddle apparatus. Accurately weighed amount 100mg of samples(F1,F2,F3) was taken for dissolution studies. The dissolution test was performed using 900 ml using pH 1.2 0.1 N Hcl at 37 ± 0.5°C. The speed of rotation of paddle was set at 75 rpm. The dissolution tests were carried out with sampling time intervals of 5, 15, 30, 45, and 60 min respectively. The samples were analyzed using a double beam UV-spectrophotometer and the absorbance was recorded at 205 nm. The in-vitro dissolution studies were tabulated.

Table no12: dissolution studies

S.No	**Time in Minutes**	**% Drug Release**		
		F1	**F2**	**F3**
1	5 min	8.12	21.78	22.18
2	15 min	20.35	34.57	33.42
3	30 min	24.12	43.76	39.72
4	45 min	32.83	59.58	54.27
5	60 min	38.57	76.14	68.12

FORMULATION OF TABLETS

The Roxithromycin Tablets were prepared by Direct Compression method per the given formula in Table

Formulation

Stage-1: The Roxithromycin Powder was sifted through 40 # mesh.

Stage-2: All the materials required as per the formulae were blended in a closed polyethylene bag and mixed well.

Stage-3: The blends were sifted through 20# mesh.

Stage-4: The lubrication materials Starch talc, and magnesium stearate were sifted through 40# mesh and added into the sifted granules and lubricated.

Stage -5: The blend is compressed into tablets by using Rotary tablet compression machine After the compression of tablets were tested for physical parameters.

Table no13: Formulation of Tablet

Ingredients	**F4**	**F5**	**F6**
Roxithromycin	75 mg	75 mg	75 mg
Micro crystalline Cellulose	110 mg	110 mg	110 mg
Sodium Starch Glycolate	15 mg	15 mg	15 mg
Talc	4 mg	4mg	4 mg
Magnesium Sterate	1 mg	1 mg	1 mg

F4-Pure Drug

F5- Choloroform Solvate (Fresh Solvate)

F6 –Choloroform Solvate (3 months Old)

EVALUATION OF FABRICATED TABLETS:

Physical characteristics of formulated tablets were evaluated for tablet size, hardness, friability, and weight variation.

Hardness:

The hardness of the tablet was tested by using Pfizer hardness tester. The results was shown in Table No-

Friability:

It was done in Electro lab friabilator apparatus where the tablets were subjected to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25rpm dropping the tablets at a distance of six inches with each revolution. Preweighed samples of 20 tablets were placed in the friabilator, which is then operated for 100 revolutions. The tablets are then dusted and reweighed. Conventional compressed tablets that lose less than 0.5 to 1.0 of their weight as generally considered acceptable. The results were shown in Table No-12.

$$\text{Friability} = \frac{W1-W2}{W1} \times 100$$

Weight Variation Test

Twenty tablets were randomly selected form each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more then two of the individual tablet weight deviate from the average weight by more than the percentage shown in Table, and none deviate by more than twice the percentage shown. The results were shown in Table.

Table No.14 Weight Variation Tolerance for Tablet (USP)

Percentage deviation allowed under weight variation test.	
Average weight of tablet (X mg)	Percentage deviation
X < 130 mg	10
130 < X < 324 mg	7.5
X > 324 mg	5

Percentage deviation allowed under weight variation test.

The observations of weight variation test of each batch are shown in Table No: 15.

Disintegration Test:

The tablets were taken in a rigid basket rack assembly supporting six cylindrical glass tubes. The assembly was suspended in the liquid medium in a 1000 ml beaker. The volume of liquid was such that, wire mesh at its lower point was at 25 mm below the surface of the liquid and its lower point was at 25 mm above the bottom of the beaker. A temperature was maintain at 37 ± 2^0C. Finally the average disintegration time was recorded.

The value of the disintegration time of all the batches given in the Table No-15

Drug content Uniformity:

5 tablets were powdered and powder equivalent to 75mg of drug was weighed and taken in a 50ml volumetric flask volume was made with Phosphate Buffer pH 6.0. The filtered using 0.2 µ membrane filter. From filtrate, 10 ml of solution was pipette out and diluted up to 100 ml with the phosphate buffer pH 6.0, and absorbance was measured at 205 nm using UV double beam spectrophotometer

The value of the disintegration time of all the batches given in the Table No-15

Table No:15 EVALUATION OF FABRICATED TABLETS:

Formulation code	Disintegration Time (in minutes)	Hardness Kg/Cm^2	Weight Variation	Friability (%w/w)	% Drug Content
F4	4.00	4.5	199	0.12	97.25
F5	4.23	4.2	203	0.16	98.13
F6	4.12	4.0	200	0.13	96.54

IN-VITRO DRUG RELEASE

In-vitro drug release study was performed using type 1 of IP (paddle) at a speed of 100 rpm. The medium was Phosphate buffer 6 (900 ml) maintained at $37^{o}C \pm 0.5^{o}C$. The dissolution test was conducted for 45 minutes; samples of 5 ml were withdrawn in the interval of 10,20,30,45 minutes with replacement of equal volume of dissolution medium. The withdrawn samples were filtered and the concentration of Roxithromycin was measured by determining absorbance at 205 nm using UV spectrophotometer.

S.No	Time in Minutes	% Drug Release		
		F4	F5	F6
1	10 min	25.49	31.57	24.28
2	20 min	39.83	47.49	35.61
3	30 min	50.52	61.25	49.85
4	45 min	62.75	76.58	64.31
5	60 min	72.08	88.14	71.25

Table No16: IN-VITRO DRUG RELEASE

RESULTS AND DISCUSSION

RESULTS AND DISCUSSION

Roxithromycin has only 50% oral bioavailability, due to its poor aqueous solubility, which limits its potential for optimal drug delivery and therapeutic effect. The aim of this study to enhance the solubility of Roxithromycin by using its solvates.

Identification of Drug:

The drug were identified using FTIR Spectra.

Phsyical Characterisation:

Solubility Studies:

From the solubility studies it was found that roxithromycin have better solubility in Phosphate Buffer pH 6 compared to other solvents.Solubility of roxithromycin is on the below order.

Water < 0.1 N Hcl < Phosphate Buffer pH 6

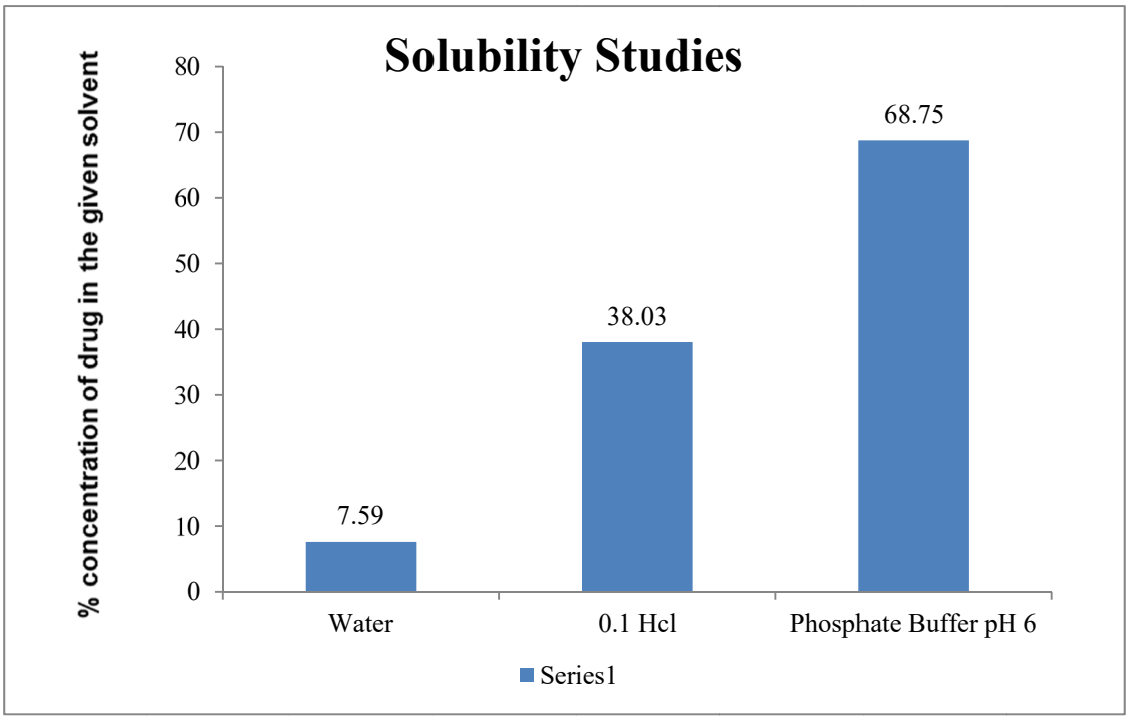


Figure no. 23. Solubility Studies of Roxithromycin

Preformulation Studies of Roxithromycin:

Bulk density, tap density, obtained bulk density and tap density values, loss on drying, compressibility index was calculated. The drugare poor flow and low compressibility. Good flow of powder /granules is essential in tableting because the flow property and compressibility is likely to influence the compression process in the preparation of tablets. The moisture content has influence on solubility & Formulation process in various aspects like sticking and also affects the moisture sensitivity drugs. The LOD for Roxithromycin was 2.2 %.

Preparation of Roxithromycin Solvates:

Roxithromycin is poorly water soluble and an improvement in its solubility could result in an improvement in its bioavailability .So solvates of roxithromycin was prepared by recrystallization by using Chloroform (F2), Ethanol (F3) as solvents.

Characterization of Roxithromycin Solvates:

FTIR STUDIES:

Overlapping of F1, F2,F3 FTIR Spectra didn't show much variation in the FTIR spectra of solvated Roxithromycin (F2 ,F3) compared to Roxitromycin (F1).So It revealed that that solvates didn't cause much variation in Chemical Structure of Pure Drug.

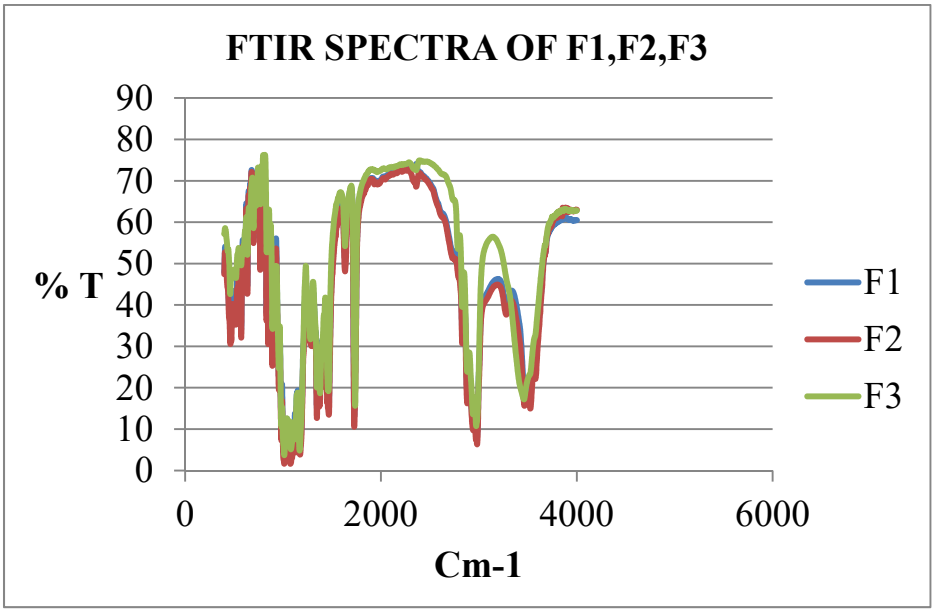


Figure no. 24. Comparative FTIR Spectra

X-ray powder diffraction (XRPD) STUDIES:

X-ray patterns of the Roxithromycin (F 1), chloroform solvate (F2) & Ethanol solvate (F 3) showed deviation in the peak heights , it is suggested that the solvated drug showed less crystalline compared to pure drug which is indicated by reduction in peak heights .In addition, on the X-ray diffraction pattern of the chloroform solvate resembles that of the amorphous solid. These results show the Reduction in crystalline of solvated drugs compared to roxithromycin Drug. Superimposed XRPD diffractograms are shown in given figure.

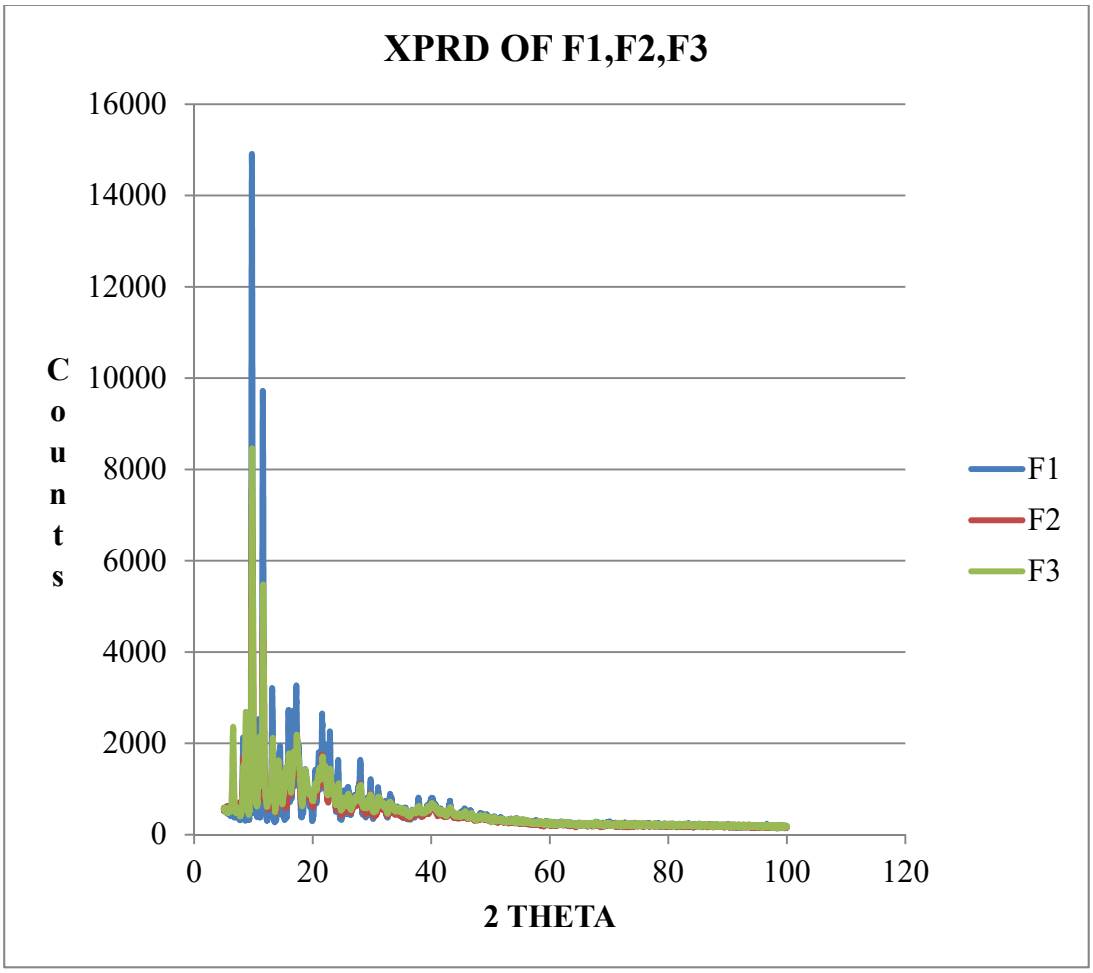


Figure no. 25. Comparative XPRD diffractogram

SEM Analysis: [SCANNING ELECTRON MICROSCOPE]

SEM microscopy images of the solvates were compared with that of the roxithromycin, It was found that the Roxithromycin(F1) has a striated appearance with more crystalline structure compared to Chloroform solvate (F 2) which has a smooth surface and Ethanol solvate (F 3) which has a partial smooth surface which was shown in given Figure.

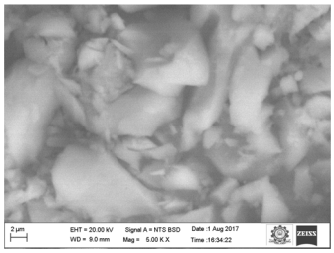
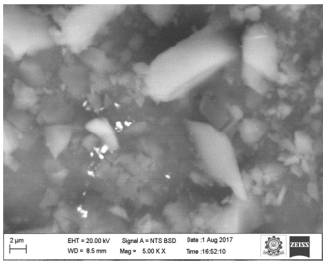
SEM of Roxithromycin	SEM of Chloroform Solvate	SEM of Ethanol Solvate
		

Figure no. 26. Comparative SEM

Aqueous Solubility Studies:

Aqueous solubility studies indicated that solvates has increased the solubility of Roxithromycin. The chloroform solvates showed better aqueous solubility compared to pure drug and ethanol solvate. The aqueous solubility was in the following order.

F1 < F3 < F2

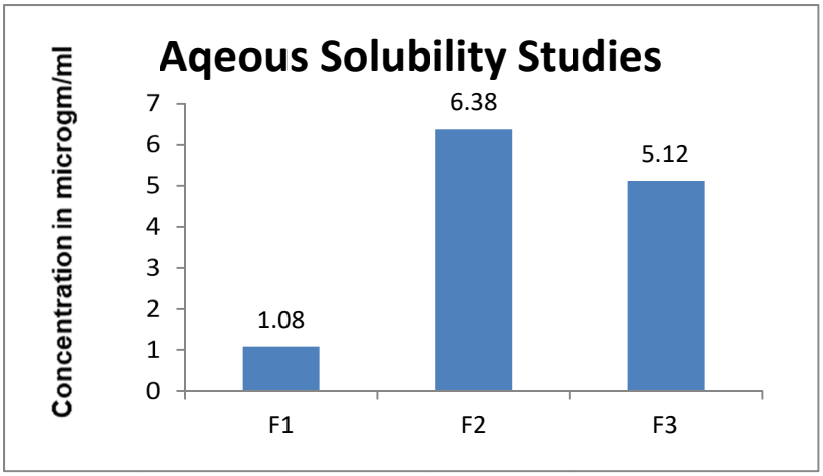


Figure no. 27. Aqueous Solubility Studies of Solvates

Dissolution Studies:

The Chloroform solvate(F2) showed better in vitro release profile compared to Pure Drug (F1) and Ethanol Solvate (F3).The Pure Drug showed a release of 38% release in 60 minutes. But solvates showed enhanced dissolution properties compared to pure drug may be due to reduction in crystalline nature of drug during salvation. The invitro release was in the following order.

F1 < F3 < F2

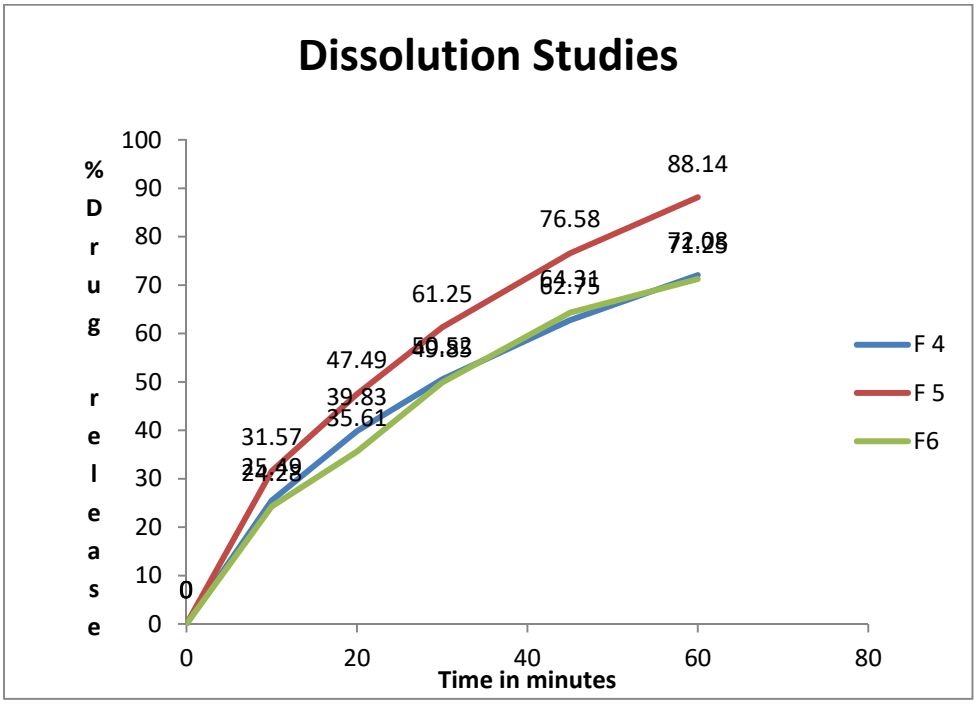


Figure no. 28. Invitro Release Profile of Solvates

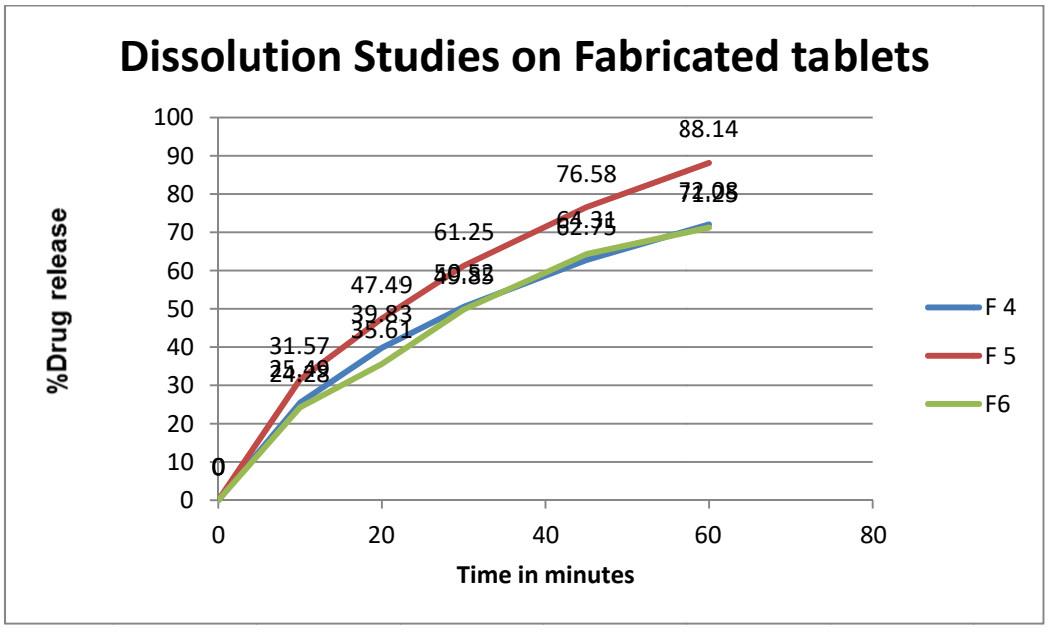
Formulation and evaluation of Tablets:

Three different batches of Roxithromycin Tablets were formulated using Pure Roxithromycin (F4), Freshly Prepared Roxithromycin Chloroform Solvate (F5) and 3 months old Roxithromycin Chloroform Solvate (F6) to find the possibilities of usage of solvates in the formulation of Dosage form and to know the ability of solvates to retain its reduced crystallinity property. Tablets were prepared by direct compression method using micro crystalline cellulose as direct compression filler and Sodium Starch Glycolate as disintegrant. The formulated tablets were evaluated for the following parameters were tabulated in the given tables.

Formulation code	Disintegration Time (in minutes)	Hardness Kg/ Cm^2	Weight Variation	Friability (%w/w)	% Drug Content	Limit
F4	4.00	4.5	199	0.12	97.25	Complies
F5	4.23	4.2	203	0.16	98.13	Complies
F6	4.12	4.0	200	0.13	96.54	Complies

Table no15: Evaluation of Fabricated Tablets:

The F 5 formulation which contained freshly prepared chloroform solvate showed better drug release profile compared to other two formulations F4 ,F6. From the *invitro* Dissolution profile it was found that F4 and F6 had similar *invitro* Drug release profile which indicated that Solvates may became more crystalline during storage. The invitro release profile was given below.



Conclusion

CONCLUSION

According to recent estimates, nearly 40% of new chemical entities are rejected because of poor solubility i.e. biopharmaceutical properties. Poor Solubility of drug may result in inadequate bioavailability and thus in ineffective treatment regimes. Similarly, roxithromycin also has a poor solubility profile and the form available on the market is mostly the stable, crystalline monohydrate with the oral bioavailability 50%.So the Objective of the present study to enhance the solubility and dissolution of Roxithromycin using solvates. Two solvate forms of roxithromycin were prepared by recrystallisation using chloroform and ethanol solvents. It was found that the Solvates showed better solubility and dissolution profile compared to Roxithromycin.Among Solvate Choloroform solvate showed better solubility and Dissolution profile than Ethanol solvate.

The tablets of Choloroform solvates were formulated by direct compression method to find the suitability of Solvates in the formulation of Pharmaceutical Dosage form by comparing Freshly Prepared Choloroform Solvates against 3 months old choloroform solvate .The variants of solvates were used to find out the stability of solvates.Based on the evaluation of tablets it was found that During storage the solvates transformed in to more crystalline substance which may affect dissolution profile from the dosage.

From the study it was concluded that Solvates can be used to enhance the solubility and dissolution of Poorly soluble drugs.

FUTURE PLAN

Solvates may be further investigated for following studies,

- Stability Studies.
- Toxicity studies
- Scale-up studies of optimized formulations
- Bioavailability studies.
- Studies of different drug candidates and their evaluation.
- In-vivo and In-vitro correlation

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